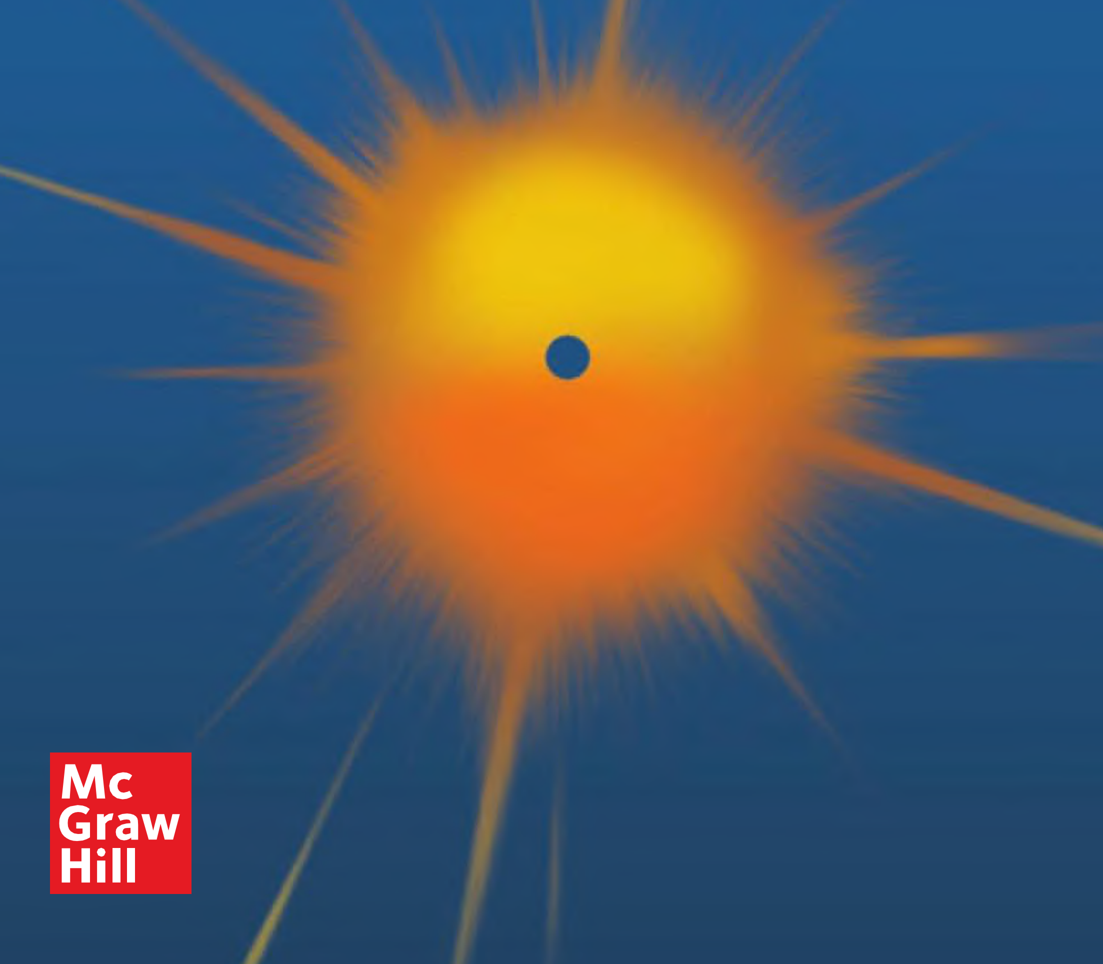
20th Edition

HARRISON'S®

PRINCIPLES OF INTERNAL MEDICINE

SELF-ASSESSMENT AND BOARD REVIEW



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For use with the 20th edition of HARRISON'S PRINCIPLES OF INTERNAL MEDICINE

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PREFACE

This is the fifth edition of *Harrison's Self-Assessment and Board Review* prepared by the Johns Hopkins team. We thank the editors of the 20th edition of *Harrison's Principles of Internal Medicine* for their continued confidence in our ability to produce a worthwhile companion to their exceptional textbook. It is truly inspirational to remind ourselves why we love medicine broadly, and internal medicine specifically.

The care of patients is a privilege. As physicians, we owe it to our patients to be intelligent, knowledgeable, contemporary, and curious. Continuing education takes many forms; many of us enjoy the intellectual stimulation and active learning challenge of the question-and-answer format. It is in that spirit that we offer the 20th edition of the *Self-Assessment and Board Review* to students, house staff, and practitioners. We hope that from it you will learn, read, investigate, and question. The questions and answers are particularly conducive to collaboration and discussion with colleagues.

This edition contains over 1000 questions and comprehensive explanations. The questions, whenever possible, use realistic patient scenarios, including radiographic or pathologic images. Our answers attempt to explain the correct or best choice, often supported with outstanding figures from *Harrison's Principles of Internal Medicine* to stimulate learning.

We have replaced more than 60% of questions from the prior edition, thus hundreds of brand new questions and explanations are included herein. We continue to try to use interesting and clinically relevant images throughout the book.

The content of this book is available in a variety of delivery formats. In addition to the print edition, an "app" will be available that offers adaptive learning features so that users can focus their studies on areas of greatest need. Several eBook formats are available, and as before the content is available on the widely used www.accessmedicine.com resource, where users can easily toggle over the Harrison's content for greater explanation and context of all the Q&A in this book. We also note that the Q&A in this book has served as the source of the Harrison's Podclass podcast for the past two years. The podcast is also available on AccessMedicine and in all the usual podcast outlets.

Although one of the authors (B.H.) has transitioned to another institution, and carries his knowledge and experience with him, he will never leave the Osler Medical Service at Johns Hopkins Hospital spiritually. Our experiences with colleagues and patients at Johns Hopkins have defined our professional lives. In the words of William Osler, "We are here to add what we can to life, not to get what we can from life." We hope this addition to your life stimulates your mind, challenges your thinking, and translates benefit to your patients. We also thank our families who cooked, minded children, and drove carpools while we toiled over this labor of love.

SECTION I

Cardinal Manifestations of Disease

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

I-1. Which of the following can help reduce errors in the delivery of health care?

A. Checklists to ensure important steps are not forgotten
B. Clinician honor code
C. Liberal use of sedatives to help patients sleep while in the hospital
D. Recommendations for handwashing
E. Use of ordering systems that rely on handwritten physician notes

I-2. All of the following statements regarding practice guidelines set forth by governing agencies and professional organizations are true EXCEPT:

A. Clinical practice guidelines protect caregivers against inappropriate charges of malpractice, yet do not provide protection for patients from receiving substandard care.
B. Practice guidelines have largely reached a stage of nuance allowing them to address every unique illness and patient presented to the modern physician.
C. Practice guidelines provide a legal constraint to physicians, and deviation from guideline-based care invariably leaves physicians vulnerable to legal action.
D. Where different organizations disagree regarding practice guidelines, a third-party agency has been appointed to mitigate these disagreements such that now all major organizations' guidelines are consistent.
E. All of the above statements are not true.

I-3. Regarding molecular medicine, which of the following statements represents an INACCURATE example of the listed area of study?

A. Exposomics: an endocrinologist studies sunlight exposure and population risk of hip fracture.
B. Metabolomics: a biochemist studies the rate of flux through the creatine kinase pathway during the cardiac cycle.
C. Metagenomics: a biologist studies the genomic alterations in molds commonly found in human dwellings.
D. Microbiomics: a microbiologist studies the genomic variation in thermophiles, which are bacteria that can survive extreme heat near deep ocean vents.
E. Proteomics: a cardiologist studies desmosomal proteins and their posttranslational modifications in studying arrhythmogenic right ventricular dysplasia.

I-4. Which of the following is the best definition of evidence-based medicine?

A. A summary of existing data from existing clinical trials with a critical methodologic review and statistical analysis of summative data
B. A type of research that compares the results of one approach to treating disease with another approach to treating the same disease
C. Clinical decision-making support tools developed by professional organizations that include expert opinions and data from clinical trials
D. Clinical decision-making supported by data, preferably randomized controlled clinical trials
E. One physician's clinical experience in caring for multiple patients with a specific disorder over many years

I-5. A 52-year-old man with no significant past medical history goes to his primary care doctor for a routine physical. His blood pressure is 119/76, pulse 75 beats/min, respiratory rate 14 breaths/min, and oxygen saturation of 99% on room air. His body mass index is 24 kg/m^2, which is increased from the prior year, and he reports that he has found it difficult to maintain a healthy weight. He continues to smoke two packs of cigarettes per day, despite attempts to quit, and does not drink alcohol. His primary care physician focuses the visit on counseling around diet and exercise to maintain a healthy weight. This counseling represents what type of prevention strategy?

A. Primary
B. Primordial
C. Secondary
D. Tertiary

I-6. All of the following screening tests are recommended by the U.S. Preventive Services Task Force for the listed patient EXCEPT:

A. Abdominal ultrasound in a 68-year-old woman with a 30 pack-year smoking history
B. Cholesterol testing in a 41-year-old woman with a normal body mass index
C. Dual-energy x-ray absorptiometry scan in a 70-year-old woman without risk factors for osteoporosis
D. Mammogram in a 56-year-old woman with no family history of breast cancer

I-7. All of the following vaccines are recommended in adults over the age of 65 EXCEPT:

A. Herpes zoster
B. Human papillomavirus
C. Influenza
D. Pneumococcal
E. Tetanus-diphtheria

I-8. You are being asked to decide whether or not a new screening test for cardiovascular disease should be approved for use. The baseline risk of mortality from cardiovascular disease in the population is 30%. With introduction of the screening test, the mortality decreases by 10%. How many people are needed to screen to prevent one death from cardiovascular disease?

A. 3
B. 6
C. 10
D. 33
E. 66

I-9. You are appointed to an advisory committee in the World Health Organization tasked with making recommendations regarding breast cancer screening and prevention. In regard to screening and preventing breast cancer in women, which of the following potential recommendations from your committee would be valid?

A. Any breast cancer detected by screening mammography and adequately treated represents a reduction in breast cancer mortality.
B. Screening is most effective when applied to relatively common diseases. Breast cancer, with a lifetime risk of 10–12% in women, meets this criterion.
C. The presence of a latent (asymptomatic) stage of breast cancer renders it a less ideal disease candidate for screening at the population level.
D. When studying the effectiveness of breast cancer screening with mammography in a population, length of disease survival is the most important outcome to consider.
E. Women in the general population should undergo just as rigorous a screening and prevention measures for breast cancer as women with the *BRCA1* or *BRCA2* mutations.

I-10. You are seeing Mr. Dallas today in the primary care clinic. He is 60 years old and has a long history of tobacco abuse but no active medical problems. You notice on his intake form that he wishes to discuss lung cancer screening today. Which of the following statements regarding lung cancer screening can you accurately make to Mr. Dallas?

A. "The U.S. Preventive Services Task Force recommends low-dose chest CT as a screening tool in patients your age with a significant smoking history."
B. "Screening for lung cancer has a long history of successful implementation given the ease of obtaining a chest x-ray and the fact that most lung cancers are curable at the time of screening detection."
C. "Screening for lung cancer is a 'no-brainer'; there is really no harm in a false-positive test. The only real worry is always that you might have a cancer that we don't know about."
D. "Because the sensitivity and specificity of any screening test do not depend on the population studied, your odds of having lung cancer after a positive chest x-ray do not depend on your smoking history."
E. "There is really no evidence of benefit for lung cancer screening by any modality."

I-11. Which preventative intervention leads to the largest average increase in life expectancy for a target population?

A. A regular exercise program for a 40-year-old man
B. Getting a 35-year-old smoker to quit smoking
C. Mammography in women age 50–70
D. Pap smears in women age 18–65
E. Prostate-specific antigen and digital rectal examination for a man >50 years old

I-12. Which of the following factors contributes to the likelihood of errors within the health care system?

A. Complexity of decision-making
B. Interruptions
C. Provider stress
D. Transitions
E. All of the above

I-13. You are conducting a review of the health outcomes of the patients in your large group practice and find that there are disparities in the pattern of referrals for kidney transplantation where minority patients with end-stage renal disease are not being referred as often as nonminority patients. One of the factors that is likely contributing to this disparity and is known to contribute to disparities in health care include:

A. Insurance status; this is, the explanation for nearly all of the disparities in care related to kidney transplant referral, and it is also found in other areas of medicine.
B. The minority patients in your practice likely declined the referral for kidney transplantation.
C. There may be an impact of race/ethnicity on clinical decision-making in the practice.
D. There was likely an error in the way the reports were pulled as it is very unlikely for this disparity to exist.

I-14. The patient is an 86-year-old man with a past medical history significant for hypertension, coronary artery disease, stroke, and peripheral vascular disease. After his last myocardial infarction, which required a prolonged intensive care unit course and hospitalization, he was sent to a rehabilitation center. His family brought him Sunday dinner and noticed that he was more confused. He is transferred to the hospital and is readmitted for further evaluation. His vital signs are notable for tachycardia with a heart rate of 134 beats/min and hypoxia with an SaO_2 of 86%. You recognize that you will need to do additional testing and will need informed consent. As part of your history and physical examination, you are trying to determine whether or not he has the capacity to make decisions for himself. You find that he is alert; oriented to person, place, time, and address; and he is able to name the president. He is able to appreciate the current situation and the consequences of his decisions. He is able to communicate a choice regarding the need for additional testing, and he seems to understand the relevant information that you have shared with him. All of the following are legally relevant criteria for establishing decision-making capacity EXCEPT the ability to:

A. Answer orientation questions that ensure he knows his name, the date, and his current location
B. Appreciate the situation and consequences
C. Communicate a choice
D. Reason about treatment decisions

I-15. All of the following are fundamental to ensuring quality palliative and end-of-life care EXCEPT the focus on:

A. Addressing psychological symptoms
B. Addressing existential or spiritual needs
C. Relieving physical symptoms
D. Treating the underlying disease
E. The social needs that include interpersonal relationships

I-16. A 72-year-old woman has stage IV ovarian cancer with diffuse peritoneal studding. She is developing increasing pain in her abdomen and is admitted to the hospital for pain control. She previously was treated with oxycodone 10 mg orally every 6 hours as needed. On admission, she is initiated on morphine intravenously via patient-controlled analgesia. She begins to complain of increased bloating and constipation since starting the increased dose of narcotics. All of the following are reasonable treatment options for her constipation EXCEPT:

A. Bisacodyl
B. Docusate
C. Fiber
D. Magnesium citrate
E. Prune juice

I-17. All of the following are components of a living will EXCEPT:

A. Delineation of specific interventions that would be acceptable to the patient under certain conditions
B. Description of values that should guide discussions regarding terminal care
C. Designation of a health care proxy
D. General statements regarding whether the patient desires receipt of life-sustaining interventions such as mechanical ventilation

I-18. A 72-year-old woman has stage IV ovarian cancer with diffuse peritoneal studding. She is developing increasing pain in her abdomen and is admitted to the hospital for pain control. She previously was treated with oxycodone 10 mg orally every 6 hours as needed. On admission, she is initiated on morphine intravenously via patient-controlled analgesia. During the first 48 hours of her hospitalization, she received an average daily dose of morphine of 90 mg and reports adequate pain control unless she is walking. What is the most appropriate opioid regimen for transitioning this patient to oral pain medication?

	Sustained-Release Morphine	Immediate-Release Morphine
A.	None	15 mg q4h as needed
B.	45 mg twice daily	5 mg q4h as needed
C.	45 mg twice daily	15 mg q4h as needed
D.	90 mg twice daily	15 mg q4h as needed
E.	90 mg three times daily	15 mg q4h as needed

I-19. You are asked to consult on a 62-year-old man who was recently found to have newly metastatic disease. He was originally diagnosed with cancer of the prostate 5 years previously and presented to the hospital with back pain and weakness. An MRI demonstrated bony metastases to his L2 and L5 vertebrae with cord compression at the L2 level only. On bone scan images, there was evidence of widespread bony metastases. He has been started on radiation and hormonal therapy, and his disease has shown some response. However, he has become quite depressed since the metastatic disease was found. His family reports that he is sleeping for 18 or more hours daily and has stopped eating. His weight is down 12 lb over 4 weeks. He expresses profound fatigue, hopelessness, and a feeling of sadness. He claims to have no interest in his usual activities and no longer interacts with his grandchildren. What is the best approach to treating this patient's depression?

A. Do not initiate pharmacologic therapy because the patient is experiencing an appropriate reaction to his newly diagnosed metastatic disease.
B. Initiate therapy with doxepin 75 mg nightly.
C. Initiate therapy with fluoxetine 10 mg daily.
D. Initiate therapy with fluoxetine 10 mg daily and methylphenidate 2.5 mg twice daily in the morning and at noon.
E. Initiate therapy with methylphenidate 2.5 mg twice daily in the morning and at noon.

I-20. You are treating a 76-year-old woman with Alzheimer's disease admitted to the intensive care unit for aspiration pneumonia. After 7 days of mechanical ventilation, her family requests that care be withdrawn. The patient is palliated with fentanyl IV at a rate of 25 μg/h and midazolam IV at 2 mg/h. You are urgently called to the bedside 15 minutes after the patient is extubated because the patient's daughter is distraught. She states that you are "drowning" her mother and is upset because her mother appears to be struggling to breathe. When you enter the room, you hear a gurgling noise that is coming from accumulated secretions in the oropharynx. You suction the patient for liberal amounts of thin salivary secretions and reassure the daughter that you will make her mother as comfortable as possible. Which of the following interventions may help with the treatment of the patient's oral secretions?

A. Increased infusion rate of fentanyl
B. *N*-Acetylcysteine nebulized
C. Pilocarpine drops
D. Placement of a nasal trumpet and oral airway to allow easier access for aggressive suctioning
E. Scopolamine patches

I-21. You are caring for a 68-year-old man with end-stage idiopathic pulmonary fibrosis. His performance status is currently 0; he is bedbound and starting home hospice care. He is chronically on nasal oxygen at 4 L/min with an SaO_2 of 94%. The patient reports relentless and severe dyspnea that has worsened over the last 1–2 months. It is now his most notable complaint. Physical examination is notable for normal vital signs other than a respiratory rate of 25 breaths/min. There is no evidence of ongoing infection or other acute pulmonary process. Which of the following interventions would be a reasonable first step to improve comfort for this patient?

A. Albuterol
B. Codeine
C. Increase nasal oxygen to 8 L/min
D. Lorazepam
E. Nebulized morphine

I-22. All of the following statements regarding euthanasia or physician-assisted suicide (PAS) are true EXCEPT:

A. Over 70% of patients with terminal disease consider euthanasia or PAS for themselves.
B. Over 75% of patients who seek PAS identify loss of autonomy or dignity and inability to engage in enjoyable activities as their main reason.
C. Patients with cancer are the most common to consider euthanasia or PAS for themselves.
D. PAS is legal in some states in the United States.
E. Voluntary active euthanasia is not legal in the United States.

I-23. The pain produced by a gentle stimulus, like a warm shower on sunburned skin, is an example of which of the following:

A. Central sensitization
B. Convergence-projection
C. Peripheral sensitization
D. Referred pain

I-24. A 75-year-old man comes to the clinic for his yearly visit. He complains of pain in his feet and ankles bilaterally that has been present for over a year. His past medical history is significant for long-standing hypertension treated with lisinopril and type 2 diabetes mellitus (hemoglobin A1c 10.3%). He lives alone and does not have any family that checks on him routinely. He works in a factory, frequently standing for most of the day, and recently the pain has limited his work capacity. He feels the pain in his feet has become debilitating and he is hoping for some relief to be able to return to work. Which of the following medications would be best for him?

A. Amitriptyline
B. Doxepin
C. Duloxetine
D. Nortriptyline

I-25. Substance P, which is released from primary afferent nociceptors, has all of the following biological activities EXCEPT:

A. Chemoattractant for leukocytes
B. Degranulation of mast cells
C. Increase intracellular concentration of cyclic guanosine monophosphate
D. Increase the production and release of inflammatory mediators
E. Vasodilation

I-26. A 28-year-old woman has had pain and redness in her left hand for the last 3 months since falling and stopping the fall with that hand. Immediate radiographs showed no fracture. Over the last few days, she has developed forearm burning and edema. Range of motion is limited at her left shoulder and left wrist. She is unable to raise her arm above the level or her head or close her left hand. She also reports allodynia to touch over the back of her left hand. Her rheumatologic and radiographic evaluation has been unrevealing. She has no past medical history; is not sexually active; takes no medications; and does not use tobacco, alcohol, or illicit drugs. Which of the following is the most likely diagnosis?

A. Acute gonococcal arthritis
B. Carpal tunnel syndrome
C. Complex regional pain syndrome
D. Gout
E. Systemic lupus erythematosus

I-27. Which of the following statements regarding cyclooxygenase (COX) inhibitors is true?

A. Aspirin is a reversible inhibitor of COX-2.
B. COX-2-selective nonsteroidal anti-inflammatory drugs (NSAIDs) are contraindicated after surgery because they inhibit platelet aggregation.
C. COX-2-selective NSAID inhibitors have a lower risk of nephrotoxicity than nonselective NSAIDs.
D. Gastrointestinal irritation is the most common side effect of aspirin and NSAIDs.
E. NSAIDs may cause a decrease in blood pressure.

I-28. A 38-year-old woman is brought to the emergency department by her spouse because of decreased mental status. She had knee surgery 2 days ago and was prescribed oral oxycodone for pain. Her spouse notes that she finished the entire 7-day supply during that day. He denies any seizure activity. They have no other drugs or medications in the house. She is afebrile with a blood pressure of 130/75, heart rate of 70 beats/min, respiratory rate of 4 breaths/min, and an SaO_2 of 85% on room air. She barely responds to painful stimuli but moves all four extremities equally. Which of the following medications is most likely to improve her mental status?

A. Albuterol
B. Alvimopan
C. Flumazenil
D. *N*-Acetylcysteine
E. Naloxone

I-29. A 66-year-old woman with a history of a previous myocardial infarction (MI) 3 years ago, hypertension, and hyperlipidemia presents to the emergency room because of new-onset chest pain. The pain is described as pressure-like in quality and located just below the left breast. The pain radiates down the left arm and to both shoulders. She has never had pain like this before. Which of the following is associated with a decreased likelihood of acute MI?

A. Inframammary location
B. Pressure-like sensation of pain
C. Radiation to left arm
D. Radiation to both shoulders

I-30. Your mother calls you late at night saying that your 63-year-old Uncle Albert went to the emergency department (ED) because of chest pain. She knows nothing more about the story or Uncle Albert's past medical history, but she is convinced he is going to die of a heart attack and wants to know what could happen. In addition to telling her to calm down, you tell your mother that:

A. Uncle Albert is more likely to have chest wall pain than ischemic cardiac disease.
B. Less than one-third of patients going to the ED with nontraumatic chest pain are found to have ischemic cardiac disease.
C. There is less than 25% chance he will be admitted to the hospital.
D. There is over a 60% chance the pain has a gastrointestinal source.
E. This is the most common reason patients go to the ED.

I-31. A 48-year-old man comes in with acute, sudden onset of headache. The pain came on suddenly during the day while working at his desk, is severe (10 out of 10 in severity) in nature, and has not let up over the last 4 hours. He has never had any pain like this before. Past medical history is notable for hypertension and hyperlipidemia. He has a temperature of 37.9°C (100.2°F), heart rate of 108 beats/min, blood pressure of 148/88, respiration of 14 breaths/min, and SaO_2 of 98% on room air. He is alert and oriented, and there are no focal neurologic deficits. Initial labs with complete blood count and comprehensive metabolic panel are within normal limits. You order a noncontrast CT scan of his head that returns normal. What is the next best test?

A. Additional laboratory testing, including erythrocyte sedimentation rate
B. Lumbar puncture
C. Ophthalmic examination
D. Temporal artery biopsy

I-32. In a patient complaining of headache, which of the following aspects of the history is worrisome and suggests further evaluation?

A. First severe headache
B. Onset after age 55
C. Pain associated with local tenderness
D. Subacute worsening over days or weeks
E. All of the above

I-33. All of the following are reasonable treatments for neck pain without radiculopathy EXCEPT:

A. Acupuncture
B. Exercise
C. Massage
D. Spinal manipulation

I-34. A 42-year-old man seeks attention for acute-onset back pain that occurred while lifting heavy boxes. He reports the pain is localized to the right lower back, radiates to the buttocks and posterior thigh, worse with standing, and improved with lying down. His medical history is only notable for hyperlipidemia for which he takes atorvastatin. His vital signs are normal, and the only positive examination finding is that raising his right leg straight while supine recreates the pain exactly at approximately 30 degrees. There are no motor or sensory defects, and reflexes are normal. Which of the following lumbosacral nerve roots is likely involved in this process?

A. L1
B. L2
C. L3
D. L4
E. L5

I-35. For the patient described in question I-34 all of the following treatments may be indicated EXCEPT:

A. Acetaminophen
B. Bedrest
C. Epidural glucocorticoid injection
D. Naproxen
E. Resumption of normal activities

I-36. A 68-year-old woman complains of worsening back, buttock, and bilateral upper leg pain over the last 6–9 months. She reports the pain is worse when she is standing for more than 10–15 minutes. The pain is also present during prolonged walking. In all cases, she feels better when she sits down. She denies any calf pain or swelling. Her medical history is notable for hypertension controlled with enalapril. Her only other medication is daily vitamin D. Her physical examination is unremarkable with normal vital signs, no lower extremity swelling, and no vascular bruits. Which of the following is the most likely diagnosis?

A. Aortic dissection
B. Lumbar disk disease
C. Lumbar spinal stenosis
D. Takayasu arteritis
E. Vascular claudication

I-37. In the patient described in question I-36, treatment may include all of the following EXCEPT:

A. Acetaminophen
B. Epidural corticosteroid injection
C. Exercise
D. Nonsteroidal anti-inflammatory drugs
E. Surgery

I-38. The patient is a 38-year-old man seeking attention for new-onset lower back pain. The pain started after he played basketball with his teenage nephews and has not resolved in the past 5 days. His mobility is limited, and the pain improves with lying down. The pain is localized to the left lumbar region and does not radiate. He takes no medications. His physical examination is normal except for pain in the involved area. There are no sensory, motor, or reflex deficits, and his straight and crossed-leg raise tests do not reproduce the pain. Which of the following is indicated at this time?

A. CT myelogram
B. Continuation of normal activities
C. MRI of the spine
D. Plain films of the back
E. Protein electrophoresis

I-39. In the patient described in question I-38, which of the following is considered evidence-based therapy at this time?

A. Cyclobenzaprine
B. Gabapentin
C. Ibuprofen
D. Prednisone
E. Tramadol

I-40. Which of the following most accurately describes hyperthermia compared with fevers?

A. Hypothalamic temperature setting is increased in fever, whereas it remains unchanged in hyperthermia.
B. In hyperthermia, the skin is usually cool to touch, whereas in febrile illnesses the skin tends to be warm.
C. Pyrogenic molecules contribute to both hyperthermia and fever.
D. Response to antipyretics such as acetaminophen and aspirin is seen in both.

I-41. A 6-year-old comes to clinic with a sore throat and fever to 39.2°C (102.5°F). She has a history of one febrile seizure 2 years ago. All of the following interventions may be appropriate EXCEPT:

A. Oral acetaminophen
B. Oral aspirin
C. Oral ibuprofen
D. Rectal acetaminophen

I-42. An 18-year-old boy from New York City presents to the student health clinic with a fever, joint pain, and a rash. The rash started with discrete lesions at his posterior hairline and then spread caudally. On physical examination there are no lesions seen at the hairline, but you do note erythematous lesions further caudally. You also note postauricular adenopathy and palatal petechiae. What additional history will help narrow the diagnosis?

A. Vaccination status for rubella (German measles)
B. Vaccination status for rubeola (measles)
C. Recent changes in medications
D. Recent travel with exposures to tick bites
E. Sexual history

I-43. An 18-year-old boy presents with 6 weeks of fatigue, fever, rash, headache, cough, and myalgias. He was previously seen in urgent care after 2 weeks of symptoms and prescribed a course of antibiotics without any improvement in symptoms. He denies any recent travel or sick contacts. He is up to date with all of his vaccinations. His vital signs are notable for a temperature of 38.5°C (101.3°F), heart rate of 105 beats/min, blood pressure of 110/65, respiratory rate of 18 breaths/min, and an SaO_2 of 97% on room air. His oral examination is shown in Figure I-43. The patient is at risk for developing which of the following in the future?

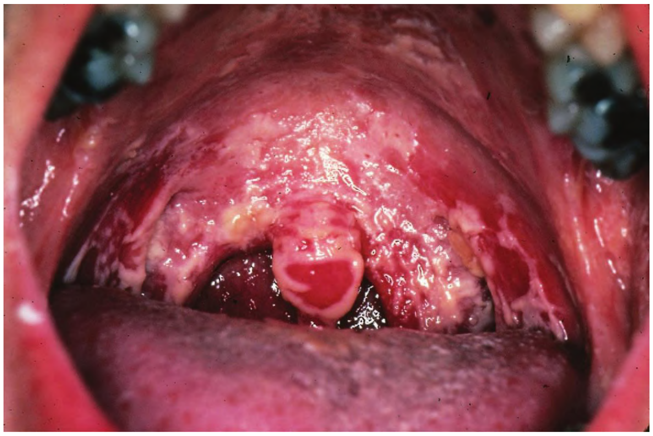


FIGURE I-43

A. Encephalitis
B. Epiglottitis
C. Opportunistic infections
D. Postherpetic neuralgia
E. Splenic rupture

I-44. A 47-year-old woman presents with a fever and rash that extends to her palms and soles. After additional history and physical, the patient is promptly admitted due to the high mortality rate associated with the presumed causative agent. Which pathogen is likely responsible for this patient's disease?

A. Chikungunya
B. Coxsackievirus A16
C. Enterovirus 71
D. *Rickettsia rickettsii*
E. *Treponema pallidum*

I-45. All of the following are causes of a urticarial rash with hives EXCEPT:

A. Hypersensitivity reaction to an allergen
B. Lymphoma
C. Parasitic infection
D. Serum sickness
E. Systemic lupus erythematosus

I-46. A 23-year-old woman with a chronic lower extremity ulcer related to prior trauma presents with rash, hypotension, and fever. She has had no recent travel or outdoor exposure and is up to date on all of her vaccinations. She does not use IV drugs. On examination, the ulcer looks clean with a well-granulated base and no erythema, warmth, or pustular discharge. However, the patient does have diffuse erythema that is most prominent on her palms, conjunctiva, and oral mucosa. Other than profound hypotension and tachycardia, the remainder of the examination is nonfocal. Laboratory results are notable for a creatinine of 2.8 mg/dL, aspartate aminotransferase of 250 U/L, alanine aminotransferase of 328 U/L, total bilirubin of 3.2 mg/dL, direct bilirubin of 0.5 mg/dL, international normalized ratio of 1.5, activated partial thromboplastin time of 1.6× control, and platelet level of 94,000/μL. Ferritin is 1300 μg/mL. The patient is started on broad-spectrum antibiotics after appropriate blood cultures are drawn and resuscitated with IV fluid and vasopressors. Her blood cultures are negative at 72 hours; at this point, her fingertips start to desquamate. What is the most likely diagnosis?

A. Juvenile rheumatoid arthritis
B. Leptospirosis
C. Staphylococcal toxic shock syndrome
D. Streptococcal toxic shock syndrome
E. Typhoid fever

I-47. A 42-year-old surveyor from Connecticut presents with a 2-day history of the rash seen in Figure I-47.

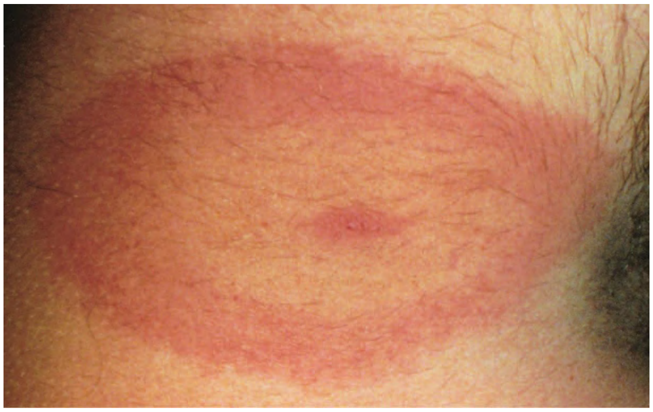


FIGURE I-47 Used with permission from Vijay K. Sikand, MD.

Which of the following signs or symptoms is also likely to develop in this patient?

A. A holosystolic murmur loudest at the cardiac apex and radiating to the axilla
B. A fissured lip, strawberry tongue, and coronary aneurysms
C. Bradycardia with an electrocardiogram finding of complete atrioventricular dissociation
D. Diffuse exanthematous rash with eventual desquamation of the hands and feet
E. White macular spots with an erythematous halo on the oral buccal mucosa

I-48. A 32-year-old man with a history of epilepsy presents to the emergency department after having a seizure. He is on maintenance levetiracetam for seizure prophylaxis at home and has been taking his medications as prescribed. In the emergency department, he has another generalized tonic-clonic seizure and is postictal after the event. He is given a dose of phenobarbital and admitted to the hospital. Over the ensuing 24 hours, a diffuse skin eruption, as depicted in Figure I-48, developed, which demonstrates early desquamation. He also developed hypotension requiring escalating vasopressor support, facial edema, generalized lymphadenopathy, abnormal liver function tests, and hepatomegaly. Differential on his completed blood count is neutrophils 72%, lymphocytes 10%, eosinophils 17%, monocytes 1%, and basophils none detected. Which of the following is the most likely diagnosis?

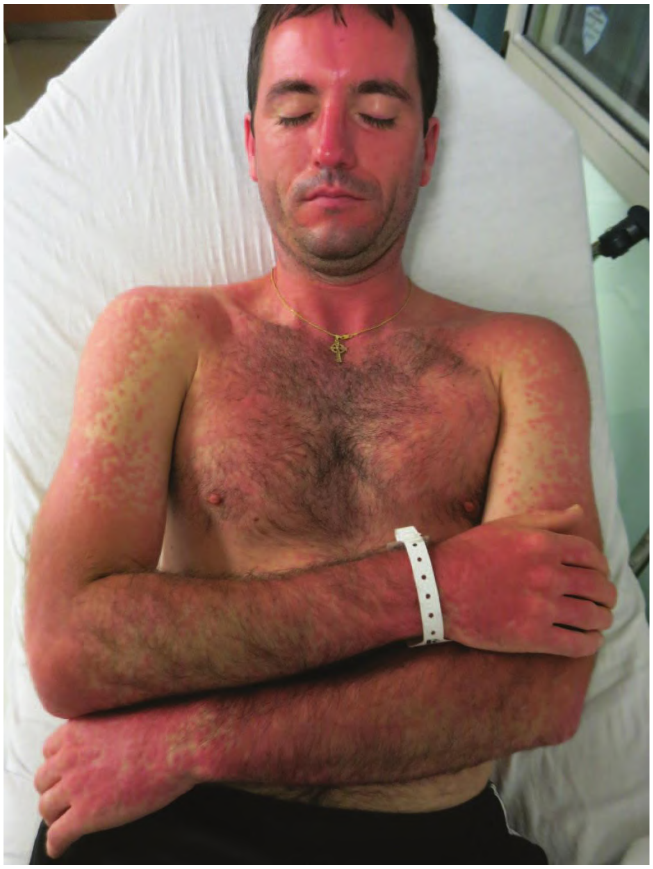


FIGURE I-48

A. Drug reaction with eosinophilia and systemic symptoms
B. Eosinophilic non-Hodgkin lymphoma with sweet syndrome
C. Erythema multiforme
D. Staphylococcal toxic shock syndrome
E. Stevens-Johnson syndrome

I-49. A 27-year-old man presents for evaluation of the skin lesions pictured in Figure I-49. On examination, he has deep-seated, painful nodules and plaques on his lower extremities.

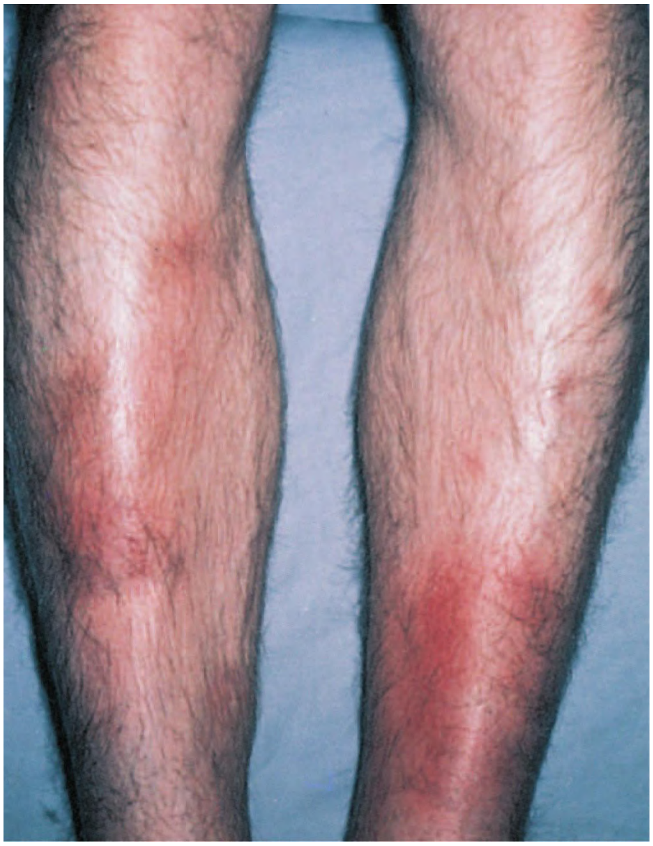


FIGURE I-49 Used with permission from Robert Swerlick, MD.

All of the following diseases are classically associated with this skin finding EXCEPT:

A. Drug exposure
B. Inflammatory bowel disease
C. Lung adenocarcinoma
D. Mycobacterial infection
E. Sarcoidosis

I-50. You review your upcoming daily clinic patients and note that you have quite a group this morning. Which of the following patients scheduled to see you today warrants the diagnosis of fever of unknown origin?

A. A 29-year-old man whom you saw 3 weeks ago. At that time, he had 1 week of twice-daily fever to 39.2°C (102.5°F), rigors, and a sore throat. He has since recovered and is asymptomatic and he is here to follow up. No cause was found for previous fevers.
B. A 29-year-old woman who has had 4 weeks of fevers to 38.4°C (101.1°F) and arthritis. Two weeks ago she developed a facial rash. One week ago she also developed oral ulcers. Lab work done during that visit was notable for an antinuclear antibody (ANA) titer above the reference range to 1:80. All other serologic testing was within normal range.
C. A 29-year-old man with fevers and rigors at home that occur at least once a day for the past month. He has never checked his temperature. Temperature in clinic today is 38.1°C (100.5°F).
D. A 29-year-old man with melanoma that was treated with immune checkpoint inhibitors and complicated by immune-related colitis for which he was started on 60 mg prednisone 6 weeks ago. For the past 3 weeks he has been having fevers to 38.5°C (101.3°F). Evaluation so far included unrevealing erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels, complete blood count, electrolytes, lactate dehydrogenase, ferritin, ANA, rheumatoid factor, urinalysis, blood and urine cultures, CT chest/abdomen/pelvis, and tuberculin skin test.
E. A 29-year-old woman with 4 weeks of daily fevers to 38.5°C (101°F) and abdominal pain. Evaluation so far included unrevealing ESR and CRP levels, complete blood count, electrolytes, lactate dehydrogenase, ferritin, ANA, rheumatoid factor, urinalysis, blood and urine cultures, CT chest/abdomen/pelvis, and tuberculin skin test.

I-51. Which of the following statements regarding the epidemiology and prognosis of fever of unknown origin (FUO) is true?

A. FUO is typically caused by a rare disease.
B. FUO more commonly presents in younger rather than older patients.
C. In geographic areas outside of the West, the proportions of cases of FUO due to neoplasms and noninfectious inflammatory diseases are similar.
D. The proportion of patients with FUO who remain undiagnosed is higher in non-Western populations compared with Western populations.
E. FUO mortality rates have been increasing, with infectious causes accounting for the most FUO-related deaths.

I-52. A 50-year-old man is evaluated for fevers and weight loss of uncertain etiology. He first developed symptoms 3 months ago. He reports daily fevers as high as 39.4°C (103°F) with night sweats and fatigue. Over this same period, his appetite has decreased, and he has lost 50 lb compared with his weight at his last annual examination. Fevers have been documented in his primary care physician's office to as high as 38.7°C (101.7°F). He has no exposures or ill contacts. His medical history is significant for diabetes mellitus, obesity, and obstructive sleep apnea. He is taking insulin glargine 50 U daily. He works in a warehouse driving a forklift. He has not traveled outside of his home area in a rural part of Virginia. He has never received a blood transfusion and is married with one female sexual partner for the past 25 years. On examination, no focal findings are identified. Multiple laboratory studies have been performed that have shown nonspecific findings only with the exception of an elevated calcium at 11.2 g/dL. A complete blood count showed a white blood cell count of 15,700/μL with 80% polymorphonuclear cells, 15% lymphocytes, 3% eosinophils, and 2% monocytes. The peripheral smear is normal. The hematocrit is 34.7%. His erythrocyte sedimentation rate is elevated at 57 mm/h. A rheumatologic panel is normal, and the ferritin is 521 ng/mL. Liver and kidney function are normal. The serum protein electrophoresis demonstrated polyclonal gammopathy. HIV, Epstein-Barr virus, and cytomegalovirus testing are negative. Urine *Histoplasma* antigen is negative. Routine blood cultures for bacteria, chest radiograph, and purified protein derivative testing are negative. A CT scan of the chest, abdomen, and pelvis shows borderline enlargement of lymph nodes in the abdomen and retroperitoneum to 1.2 cm. What would be the next best step in determining the etiology of fever in this patient?

A. Empiric treatment with corticosteroids
B. Empiric treatment for *Mycobacterium tuberculosis*
C. Needle biopsy of enlarged lymph nodes
D. Positron emission tomography-CT imaging
E. Serum angiotensin-converting enzyme levels

I-53. Which of the following statements regarding syncope is true?

A. Neurally mediated syncope is the etiology in the vast majority of cases.
B. Orthostatic hypotension decreases in prevalence after age >70 years.
C. Syncope due to orthostatic hypotension related to age is benign and does not affect mortality.
D. Syncope is not very common, with a lifetime cumulative incidence of 1–2% in the general population.
E. The incidence of syncope declines after age 70.

I-54. A 42-year-old woman presents with the acute onset of feeling like the room is spinning over the past 2 hours. She also reports associated nausea, vomiting, oscillopsia, and a sense of imbalance. These symptoms are present with movement and at rest. On examination her vital signs are within normal limits. Head impulse test demonstrates leftward saccade after a rightward rotation. She has 5/5 strength in bilateral upper and lower extremities. Sensation is intact to light touch bilaterally. Reflexes are 2+ throughout. She has an erythematous vesicular rash noted on her external ear (Figure I-54). All of the following may be helpful for treatment of her condition EXCEPT:

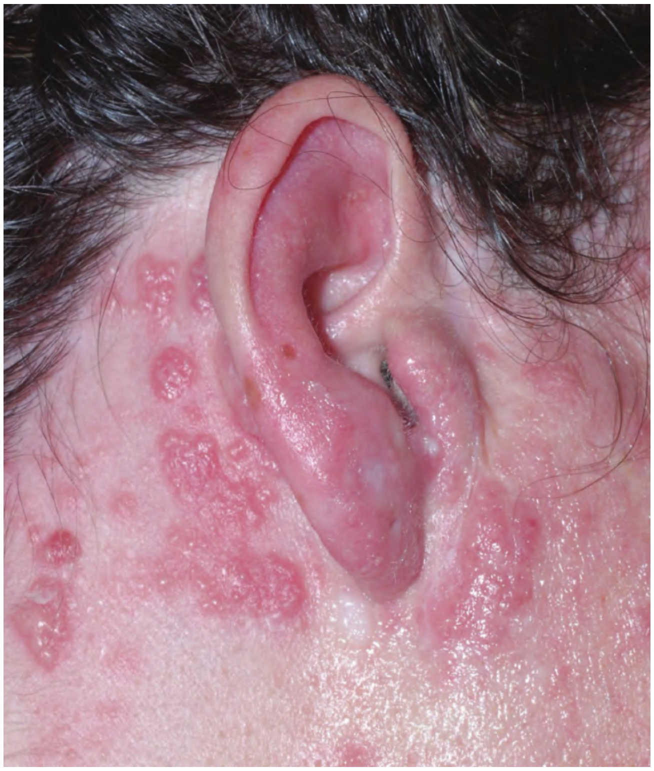


FIGURE I-54 Reproduced with permission from Knoop KJ et al: *The Atlas of Emergency Medicine*, 5th ed. New York: McGraw Hill, 2021. Photo contributor: Lawrence B. Stack, MD.

A. Antiviral therapies
B. Glucocorticoids
C. Thrombolytic therapy
D. Vestibular suppressant medications
E. Vestibular rehabilitation

I-55. A 42-year-old man presents to the emergency department complaining of severe vertiginous dizziness associated with nausea. Which of the following examination findings is most consistent with a peripheral cause of vertigo?

A. Downbeat nystagmus
B. Gaze-evoked nystagmus
C. Pure torsional nystagmus
D. Rebound nystagmus
E. Unidirectional horizontal nystagmus

I-56. A 62-year-old man presents to the clinic complaining of frequent falls. He complains of feeling “off balance.” He denies vertigo or orthostatic symptoms, but he complains that he feels unsteady, which is exacerbated in the dark or when his eyes are closed. He complains of increased difficulty focusing while moving because the world “jumps around,” and he is no longer able to read a book during his routine subway commute to work. He has no history of peripheral neuropathy or nutritional deficiency. He recently completed 6 weeks of antibiotic therapy for *Enterococcus faecalis* bacteremia with endocarditis. On examination, corrective saccades are noted bilaterally on the head impulse test. Which medication is most likely to have caused this patient’s gait instability?

A. Ampicillin
B. Ceftriaxone
C. Gentamicin
D. Penicillin
E. Vancomycin

I-57. A 29-year-old woman presents for a second opinion evaluation of chronic fatigue syndrome. She was well until 2 years ago when she developed insidious and recalcitrant weariness. She sleeps 10 hours a night but awakes feeling unrefreshed. She is unable to tolerate exercise, which only worsens her malaise, and she is no longer able to work. She has no significant past medical or psychiatric history. In addition to a detailed history and physical, which of the following is recommended as a reasonable approach to screening patients who complain of chronic fatigue?

A. Antinuclear antibody testing
B. Electromyography with nerve conduction studies
C. Epstein-Barr virus testing
D. Lyme serologies
E. Thyroid function testing

I-58 to I-60. Match the clinical presentation to the most likely origin of the weakness

I-58. A 40-year-old man, new to your clinic, presents with right arm weakness. On examination you note spastic tone and hyperactive bicep tendon reflexes.

I-59. A 40-year-old man presents with bilateral leg weakness. There is no atrophy and no fasciculations. On examination you note paratonia. Babinski sign is absent.

I-60. A 40-year-old man who has difficulty combing his hair and standing up out of bed comes into your clinic. Patellar and biceps reflexes are normal. Babinski sign is absent. He has mild atrophy noted in the proximal muscle groups.

A. Lower motor neuron
B. Myopathy
C. Psychogenic weakness
D. Upper motor neuron

I-61. A 42-year-old man presents complaining of progressive weakness over a period of several months. He reports tripping over his toes while walking and has dropped a cup of hot coffee on one occasion because he felt too weak to continue to hold it. A disorder affecting lower motor neurons is suspected. All of the following findings would be found in an individual with a disease primarily affecting lower motor neurons EXCEPT:

A. Decreased muscle tone
B. Distal greater than proximal weakness
C. Fasciculations
D. Hyperactive tendon reflexes
E. Severe muscle atrophy

I-62. A 65-year-old man with a long-standing history of hypertension presents with numbness on the right side of his face and the left side of his body. What is the most likely cause of his symptoms?

A. Brainstem lesion
B. C1 spinal cord transection
C. Cortical lesion
D. Thalamic lesion
E. Psychogenic sensory loss

I-63. A 58-year-old sedentary man presents with acute lower back pain and diminished sensation over the medial lower leg below the knee extending to the ankle. Which of the following nerve roots is most likely involved in the injury?

A. L2
B. L3
C. L4
D. L5
E. S1

I-64. All of the following sensations are mediated by unmyelinated and small myelinated afferent peripheral nerve fibers EXCEPT:

A. Cold temperature
B. Light touch
C. Pain
D. Vibration
E. Warm temperature

I-65. An 86-year-old woman is taken by ambulance to the emergency room after being found on the floor after a fall in the hallway of her assisted living facility. She has a history of osteoarthritis, hypertension for which she takes amlodipine 5 mg daily, and a remote history of a stroke with residual mild right-sided weakness. At the assisted living facility she has her meals prepared for her but is otherwise independent. She walks with a walker daily since her stroke and wears glasses only for reading. She has never had a fall before. Which of the following is the greatest risk factor for falls in this patient?

A. Age >80
B. Arthritis
C. Muscle weakness
D. Use of a walker
E. Visual deficit

I-66. A 65-year-old man presents complaining of frequent falls and gait abnormalities. He first noticed the difficulty about 6 months ago. He has a history of hypertension, hypothyroidism, and hyperlipidemia. His current medications include amlodipine 10 mg daily, simvastatin 20 mg daily, and levothyroxine 75 μg daily. On neurologic examination, you observe his gait to be wide based with short shuffling steps. He has difficulty rising from his chair and initiating his gait. On turning, he takes multiple steps and appears unsteady. However, cerebellar testing is normal including heel-to-shin and Romberg testing. He has no evidence of sensory deficits in the lower extremities, and strength is 5/5 throughout all tested muscle groups. He shows no evidence of muscle spasticity on passive movement. His neurologic examination is consistent with which of the following causes?

A. Alcoholic cerebellar degeneration
B. Communicating hydrocephalus
C. Neurosyphilis
D. Multiple system atrophy
E. Lumbar myelopathy

I-67. A 67-year-old woman is admitted for management of sepsis from a urinary source, complicated by nephrolithiasis. You are called to evaluate a change in mental status. Her husband reports that she now appears withdrawn, inattentive, and apathetic, in contrast to her normally vivacious baseline. Her bedside nurse reports that her alertness has fluctuated throughout the day and she has difficulty sleeping at night. Which of the following is least likely to be helpful for the treatment of these symptoms?

A. Antibiotics
B. Benzodiazepines
C. Pain medication
D. Reorientation with opening the blinds during the day

I-68. An 82-year-old woman was admitted to the intensive care unit 10 days ago with severe sepsis due to pneumonia complicated by renal and respiratory failure. She is supportively treated with fluid resuscitation, vasopressors, broad-spectrum antibiotics, invasive mechanical ventilation, and chemical sedation. Although initially alert, calm, and cooperative, on morning rounds the nurse reports the patient seems agitated, was awake all night, and is no longer able to answer any of the yes/no questions she previously was getting correct. Which of the following tests is the next most appropriate in the evaluation of her new symptoms?

A. Brain MRI with and without contrast
B. Head CT without contrast
C. Rapid plasma reagin
D. Serum chemistries
E. Urine toxicology

I-69. A 76-year-old previously healthy man presents to the emergency department for evaluation of an acute change in mental status. He appears agitated and is pacing the room. He has difficulty focusing his attention and provides an incoherent history. His temperature is 36.9°C (98.4°F), blood pressure is 134/72, pulse is 94 beats/min, and room-air oxygen saturation is 99%. Laboratory investigations are unremarkable. His wife reports that he has been taking over-the-counter diphenhydramine for an itchy contact dermatitis for the past 2 days. Interference with which neurotransmitter most likely precipitated this change in mental status?

A. Acetylcholine
B. Dopamine
C. Histamine
D. Norepinephrine
E. Serotonin

I-70. An 81-year-old-man with a history of atrial fibrillation and chronic alcoholism is accompanied to the clinic by his adult daughter. She reports he has had increasing memory loss over the past 5 years. She first noticed he had difficulty shopping for himself about 3 years ago and his ability to manage daily tasks has declined since then. On physical examination he has no motor deficits. There were no deficits noted on the Mini-Mental State Examination or Montreal Cognitive Assessment; however, he did score poorly when asked to name as many animals as possible in one minute. Which of the following imaging findings would be helpful to support the diagnosis?

A. Insular or temporal atrophy
B. Hippocampal atrophy
C. Multifocal white matter abnormalities
D. Restricted diffusion within the cortical ribbon
E. Gaping Sylvian fissures with minimal cortical atrophy

I-71. A 90-year-old woman is brought into the clinic by her adult son. Her son notes that she has been getting increasingly forgetful over the years. Fortunately, this has not affected her activities of daily living and she is still able to live independently, with minimal help from her son. Her son is concerned she has dementia. She says she is "just getting old." Neurologic examination and limited neuropsychological testing in your office is normal. She undergoes formal neuropsychiatric testing and is diagnosed with mild cognitive impairment (MCI). Which of the following predicts progression from MCI to Alzheimer's dementia?

A. α-Synuclein neuronal inclusions
B. Absence of apolipoprotein ε4 allele
C. Family history of dementia
D. Frontotemporal deficits on positron emission tomography-computed tomography
E. High cerebrospinal fluid Aβ

I-72. You are evaluating a previously healthy 73-year-old man with 3–4 months of cognitive decline as reported by his loving wife and daughter. They report that the patient was fully engaged in gardening and competitive board games; however, over the last 6 months, his garden has gone untended, and he expresses absolutely no interest in board games. He also has inappropriate outbursts of rage in social situations, such as in the mall. Over the last 2 months, he has gained about 15 pounds and always seems to be eating or snacking. His only medication is atorvastatin, which he has been taking for 20 years. Based on this history, you are most concerned about which of the following diagnoses?

A. Alzheimer's disease
B. Creutzfeldt-Jakob disease
C. Dementia with Lewy bodies
D. Frontotemporal dementia
E. Vascular dementia

I-73. Which of the following statements regarding Alzheimer's disease is true?

A. Delusions are uncommon.
B. It accounts for over half of the cases of significant memory loss in patients over 70 years of age.
C. It typically presents with rapid (<6 months) significant memory loss.
D. Less than 5% of patients present with nonmemory complaints.
E. Pathologically, the most notable abnormalities are in the cerebellar regions.

I-74. A 58-year-old man with a history of hypertension and poorly controlled diabetes is brought to the hospital because he was sitting with his wife at home having breakfast when all of a sudden he started saying words that did not make sense. In the emergency department, he was evaluated for acute stroke. He was found to have an embolus in the inferior division of the middle cerebral artery affecting the Wernicke area. Which of the following would you expect to find on examination?

A. Comprehension; repetition, naming impaired; fluency intact
B. Comprehension intact; repetition, naming, fluency impaired
C. Comprehension; repetition, naming, and fluency impaired
D. Comprehension and fluency intact; repetition and naming impaired

I-75. A 65-year-old man experiences an ischemic cerebrovascular accident affecting the territory of the right anterior cerebral artery. Following the stroke, an assessment reveals the findings shown in Figure I-75. Which of the following diagnoses does this figure suggest?

A. Construction apraxia
B. Hemianopia
C. Hemineglect
D. Object agnosia
E. Simultanagnosia

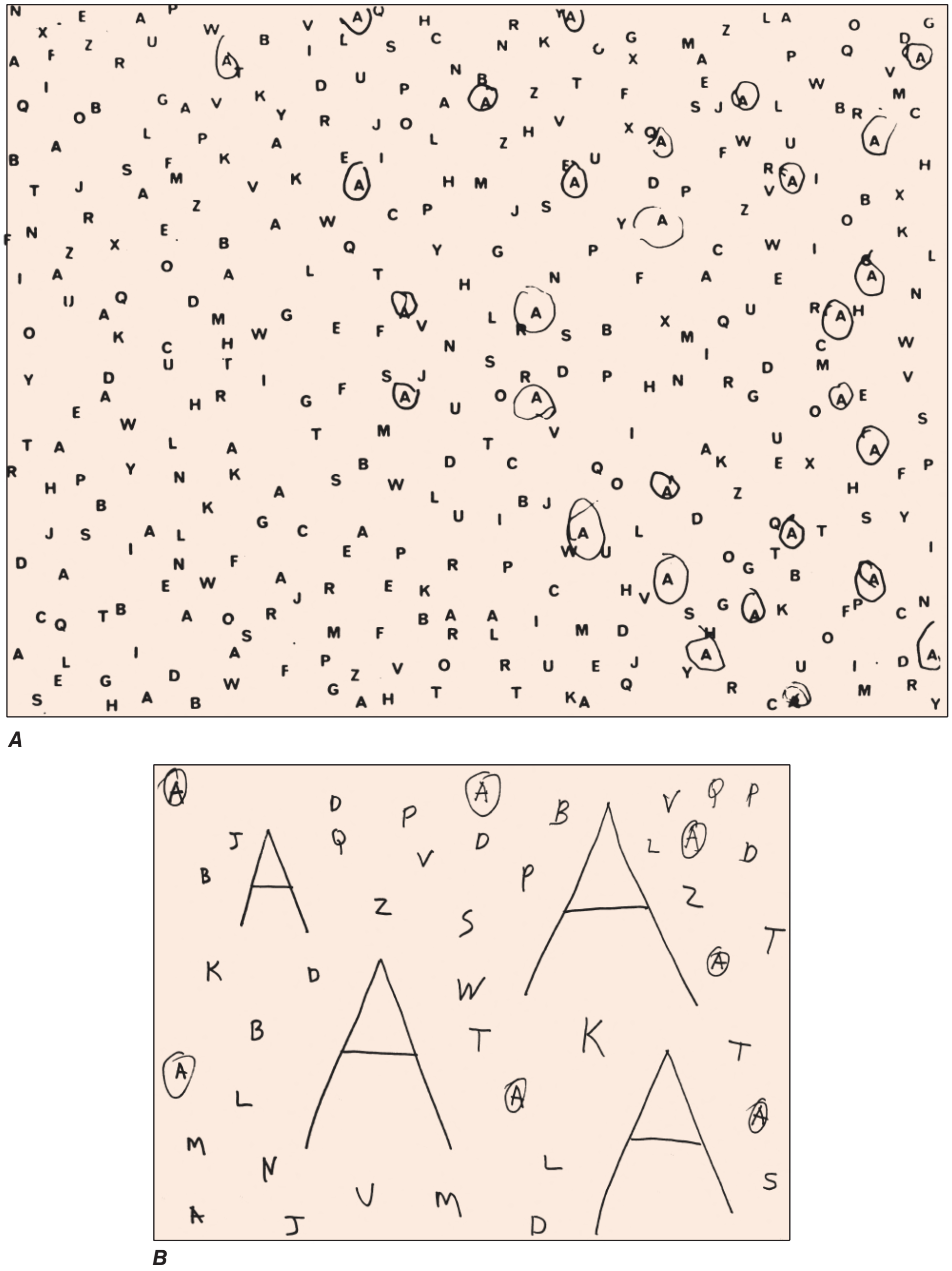


FIGURE I-75

I-76. A 74-year-old man with a history of well-treated hypertension presents with painless blurry vision on one side. You perform the "swinging flashlight" test and the results are shown in Figure I-76. Panel A shows the patient sitting in a dim room, panel B shows him with the flashlight shining in his right eye, and panel C shows the flashlight shining in his left eye. What is the likely cause of the defect shown?

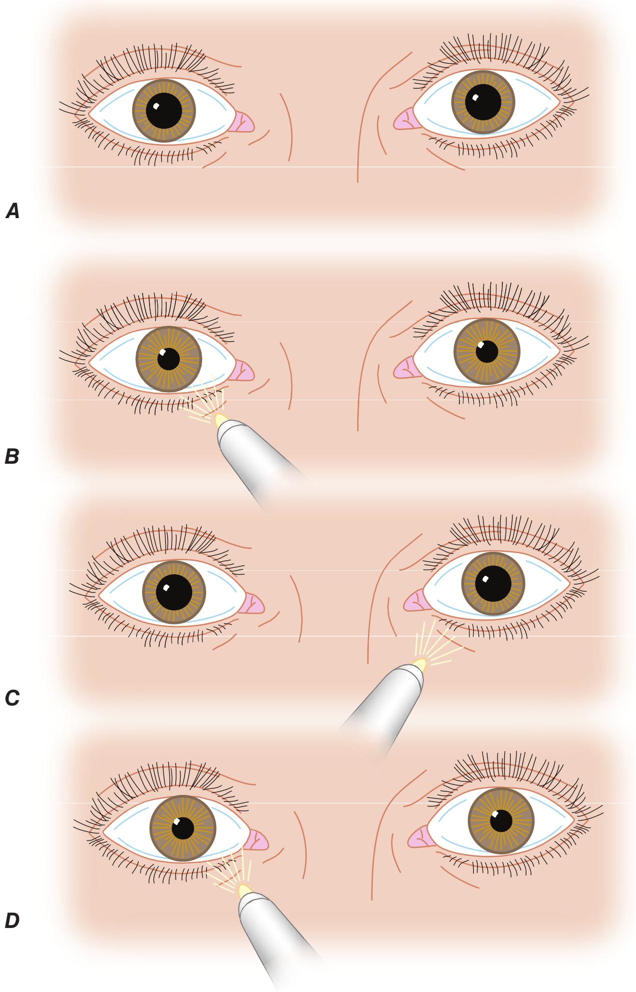


FIGURE I-76 Reproduced with permission from Tintinalli J et al: *Tintinalli's Emergency Medicine: A Comprehensive Study Guide*, 9th ed. New York: McGraw Hill, 2020.

A. Bilateral optic neuropathy
B. Optic chiasm lesion
C. Oculomotor nerve palsy
D. Left lung apical tumor
E. Left optic neuritis

I-77. A 28-year-old woman comes to the emergency room with new-onset, bilateral, severe headaches. She only takes tetracycline for acne. Her vital signs are blood pressure 124/78, heart rate 102 beats/min, SaO_2 98%, and respiratory rate 14 breaths/min. Neurologic examination is within normal limits. Ophthalmoscopy of her left eye is shown in Figure I-77.

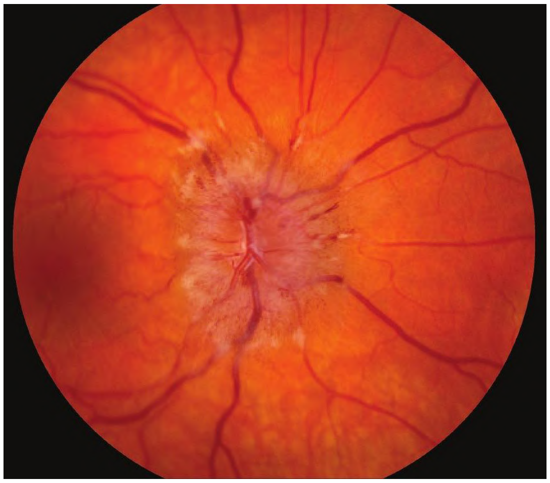


FIGURE I-77

Which of the following is the best recommendation for diagnosis and treatment?

A. Acetaminophen, aspirin, caffeine
B. Check labs for elevated glucose, start insulin
C. Check blood cultures and start empiric broad-spectrum antibiotics
D. Give high-dose steroids
E. Stop tetracycline

I-78. A 13-year-old girl with no past medical history has recently noticed that she is having trouble in school reading the board, particularly in her biology class where she sits near the back of the room. In her English literature class, where she sits in the front, she does not have nearly as much difficulty. After performing the standard tests for visual acuity, you determine that the young girl has a refractive error whereby her globe is too long, and light rays come to a focal point in front of the retina. Which term accurately describes this patient's ophthalmologic condition and is associated with the appropriate type of corrective lens?

A. Emmetropia: diverging lens
B. Hyperopia: diverging lens
C. Hyperopia: converging lens
D. Myopia: diverging lens
E. Presbyopia: reading glasses

I-79. You are seeing Mrs. Ruth today in the clinic. For the preceding 6 weeks, she has noticed no symptoms other than occasionally running into doors and walls. You perform a complete physical examination and note abnormalities in her visual fields. Testing each eye individually while gazing forward, she cannot see your fingers laterally on either side. Her vision seems appropriate nasally and to the middle in both eyes. You promptly refer Mrs. Ruth for a brain MRI. Where do you anticipate finding a lesion?

A. Left optic nerve
B. Left parietal lobe
C. Optic chiasm
D. Right occipital lobe
E. Right retina

I-80. All of the following are common causes of long-lasting or permanent loss of smell EXCEPT:

A. Aging
B. Chronic rhinosinusitis
C. Supranuclear palsy
D. Trauma
E. Upper respiratory tract infection

I-81. In what anatomical structural way is the olfactory system unique among the sensory systems?

A. Initial afferent projections bypass the thalamus and synapse directly with the primary olfactory cortex.
B. The olfactory system's primary sensory neurons uniquely are chemoreceptors.
C. Primary olfactory cortex is anatomically distant from the hippocampus and amygdala.
D. The primary sensory neuron synapses directly with the olfactory cortex.
E. Thalamic damage enacts no olfactory deficit.

I-82. All of the cranial nerves in the list are matched correctly with their innervation territory in regard to the sense of taste EXCEPT:

A. VII: anterior tongue
B. VII: soft palate
C. IX: posterior tongue
D. IX: soft epiglottis
E. X: larynx

I-83. Which of the following statements is true regarding presbyosmia and anosmia?

A. A majority of the population over the age of 80 years suffers from presbyosmia.
B. Anosmia is often a late feature of end-stage Parkinson disease.
C. Patients with trauma-related anosmia rarely recover any olfactory function.
D. While irritating, presbyosmia confers no real health risk.
E. Women suffer from presbyosmia at a greater rate than men

I-84. Mr. McEvoy is a 42-year-old long-haul truck driver who comes to your clinic for an urgent care visit. Two days ago, he noticed that his face felt unusual. While checking the rearview mirror, he noticed that the left side of his face looked different from normal. He also noticed that he drooled some of his soda, and it tasted quite odd. These symptoms did not improve over the ensuing 2 days of his trip. He denies any tick exposures or any other neurologic symptoms. On examination he has a mild left facial droop and is unable to raise the left side of his mouth when you ask him to smile. You explain to Mr. McEvoy that the most common cause of his facial paralysis and taste disturbance is viral involvement of which of the following cranial nerves?

A. V
B. VI
C. VII
D. IX
E. X

I-85. A 64-year-old man is evaluated for hearing loss that he thinks is worse in his left ear. His wife and children have told him for years that he does not listen to them. Recently, he has failed to hear the chime of the alarm on his digital watch, and he admits to focusing on the lips of individuals speaking to him as he sometimes has difficulties in word recognition. In addition, he reports a continuous buzzing that is louder in his left ear. He denies any sensation of vertigo, headaches, or balance difficulties. He has worked in a factory for many years that makes parts for airplanes, and the machinery that he works with sits primarily to his left. He has no family history of deafness, although his father had hearing loss as he aged. He has a medical history of hypertension, hyperlipidemia, and coronary artery disease. You suspect sensorineural hearing loss related to exposure to the intense noise in the factory for many decades. Which of the following findings would you expect on physical examination?

A. A deep tympanic retraction pocket seen above the pars flaccida of the tympanic membrane
B. Cerumen impaction in the external auditory canal
C. Hearing loss that is greater at lower frequencies on pure tone audiometry
D. Increased intensity of sound when a tuning fork is placed on the mastoid process compared with placement near the auditory canal
E. Increased intensity of sound in the right ear when a tuning fork is placed in the midline of the forehead

I-86. In the patient described in question I-85, which of the following should be the next suggested diagnostic test?

A. Head CT scan
B. Brain MRI with gadolinium contrast
C. Pure tone and speech audiometry
D. Schirmer test
E. Tympanometry

I-87. A 32-year-old woman presents to her primary care physician complaining of nasal congestion and drainage and headache. Her symptoms originally began about 2 weeks ago with rhinorrhea and sore throat. For the last 5 days, she has had increasing feelings of fullness and pressure in the maxillary area, which is causing her headaches. The pressure is worse when she bends over, and she notices it while lying in bed at night. She is otherwise healthy and has not had any fever. She reports an allergy to penicillin. On physical examination, there is purulent nasal drainage and pain with palpation over bilateral maxillary sinuses. What is the best approach to ongoing management of this patient?

A. Initiate therapy with doxycycline 100 mg PO bid
B. Initiate therapy with amoxicillin/clavulanate 500/12 mg PO three times daily
C. Initiate therapy with amoxicillin/clavulanate (extended release), 2000/125 mg PO bid
D. Perform a sinus aspirate for culture and sensitivities
E. Supportive care including oral decongestants and nasal saline lavage

I-88. A 63-year-old man presents to the clinic with 1 day of difficulty with speech and swallowing. He also notes pain with swallowing. He reports having a tooth pulled 3 days prior. On examination his temperature is 39.2°C (102.6°F), blood pressure 136/82, heart rate 114 beats/min, and SaO_2 100% on room air. On oropharyngeal exam, you note edema in the sublingual region and drooling. What is the best management strategy?

A. Outpatient oral prescription for amoxicillin/clavulanate 200/125 mg PO twice a day
B. Outpatient oral prescription for moxifloxacin 400 mg PO daily
C. Outpatient oral prescription for metronidazole 500 mg three times a day
D. Hospital admission for IV vancomycin
E. Hospital admission for IV ampicillin/sulbactam

I-89. An 18-year-old foreign exchange student comes to the university health clinic complaining of 1 day of fevers to 39.4°C (103°F) and severe sore throat to the point she cannot swallow her oral secretions. Her examination is notable for inspiratory stridor and respiratory distress. The lateral radiograph of her neck is shown in Figure I-89.

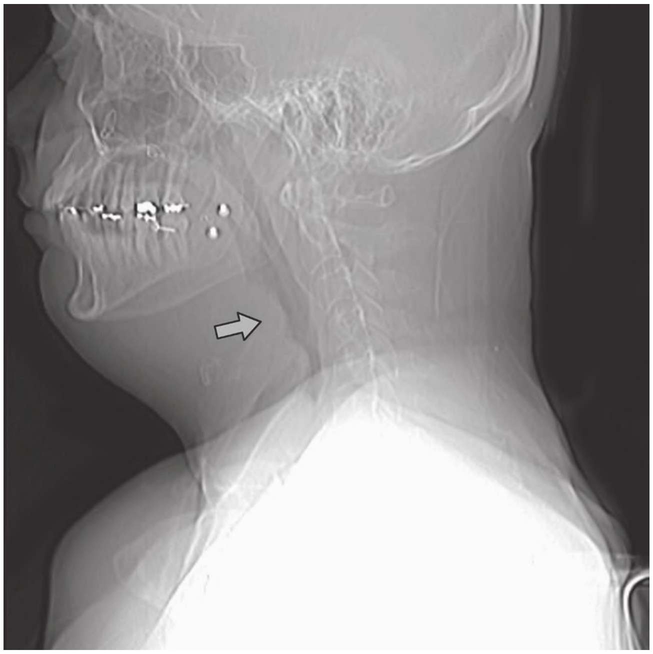


FIGURE I-89

Which of the following vaccines has decreased the incidence of this condition in children?

A. *Haemophilus influenzae* type B
B. MMR (measles-mumps-rubella)
C. Pertussis
D. Rotavirus
E. Varicella

I-90. A 19-year-old college student presents with 3 days of increasing left-sided pain below his ear and feeling feverish. He noted some nasal congestion over the last 2 weeks due to high pollen counts. The pain has worsened despite taking decongestants and acetaminophen. He has a history of allergic rhinitis and multiple episodes of otitis media. On examination, there is tenderness, some swelling at the left mastoid process, and fluid behind the left temporal membrane. Because of his history, a CT scan is obtained and is shown in Figure I-90. Which of the following is the most likely diagnosis?

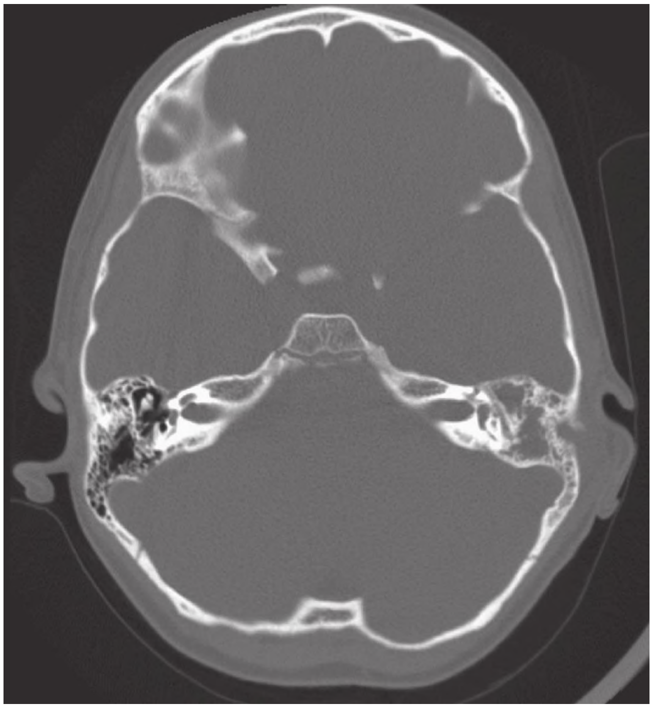


FIGURE I-90

A. Acute mastoiditis
B. Otitis externa
C. Mucormycosis
D. Meningioma
E. Septic thrombosis

I-91. A 28-year-old man seeks evaluation for a sore throat that began 2 days ago. He has not had a cough or rhinorrhea. He has no other medical conditions and works as a daycare provider. On examination, tonsillar hypertrophy with bilateral membranous exudate is present. What is the next step in the management of this patient?

A. Empiric treatment with amoxicillin 500 mg twice daily for 10 days
B. Rapid antigen detection test for *Streptococcus pyogenes* only
C. Rapid antigen detection test for *S. pyogenes* plus throat culture if rapid test is negative
D. Rapid antigen detection test for *S. pyogenes* plus throat culture regardless of result
E. Throat culture only

I-92. Which of the following is true about xerostomia or dry mouth?

A. It plays no role in other diseases.
B. Medication is not commonly a cause.
C. Preventive dental care is not a part of the management strategy.
D. Pilocarpine has been shown to increase secretions.
E. The sensation is perceived when salivary flow is reduced by 75%.

I-93. A 58-year-old man comes to the clinic for a routine physical examination. He has a history of hyperlipidemia and hypertension controlled with atorvastatin and enalapril. Despite counseling, he smokes 1 pack of cigarettes per day. On physical examination, you notice some ulcerations in the mouth below the tongue (Figure I-93). The lesions are not painful, and the patient reports no recent mouth symptoms.

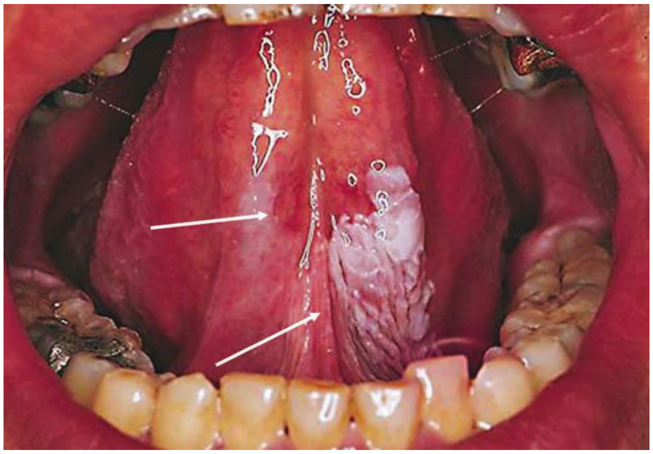


FIGURE I-93

This patient is at greatest risk of which of the following disorders?

A. Celiac disease
B. Crohn disease
C. Oral candidiasis
D. Reactive arthritis
E. Squamous cell carcinoma

I-94. All of the following symptoms described by patients are correctly matched with the mechanism underlying the cause of dyspnea EXCEPT:

A. Air hunger: central chemoreceptors in the medulla acting on the peripheral chemoreceptors in the carotid body
B. Chest tightness: stretch receptors in the lung acting on the brainstem
C. Hard to breathe: motor cortex of the brain acting on the respiratory muscles
D. Increased effort: motor cortex of the brain to the sensory cortex of the brain

I-95. Mrs. Jones is a 48-year-old woman with hypertension and obesity. She presents to your office for the second time today because of a cough. When you first saw her 2 weeks ago, she complained of a cough productive of scant sputum lasting for over 2 months. She intermittently took some over-the-counter decongestants at night, but she now returns without any diminution in her cough. Which of the following parts of the history and physical examination maneuvers is least likely to be helpful in elucidating the cause of her cough?

A. Burning chest pain that occurs most often after eating
B. Inspection of the fingernails for selective bulbous enlargement of the distal segments of the fingers and toes due to proliferation of connective tissue, particularly on the dorsal surface
C. Medication list for beta blockers as these are the most common cause of medication-induced coughs
D. Stimulation of the auricular branch of the vagus nerve in the external auditory meatus
E. Time of day her cough is the worst

I-96. You are riding the bus home after a busy clinic one day. A man sits next you and, ignoring the easily seen signs, begins to smoke a cigarette. You feel a "tickle in your throat" and then proceed to cough. All of the following statements regarding the cough are true EXCEPT:

A. During a cough, rapid expiratory flows are generated but cannot exceed the normal envelope of maximum voluntary expiratory flow seen on a spirometry or flow-volume curve assessment.
B. In initiating a cough, the vocal cords must first adduct.
C. In some patients, stimulation of the auricular branch of the vagus nerve in the external auditory meatus can stimulate a cough.
D. Pressures approaching 300 mmHg can be generated in the thorax during the cough reflex.
E. The velocity of expiratory airflow is crucial to dislodging mucus or other irritants from the airway walls.

I-97. Mr. Boyle is a 19-year-old college student with cystic fibrosis. While studying for midterm exams, he suddenly begins coughing up large volumes of bright red blood. Emergency medical personnel are rapidly called and transfer him to the nearby university hospital emergency department, where you are working. Given his medical history, you suspect his bleeding is arising from which blood vessel(s)?

A. Alveolar capillaries
B. Bronchial arteries
C. Gastric varices
D. Pulmonary artery
E. Pulmonary veins

I-98. The patient described in question I-97 is coughing up large volumes of blood as he is wheeled into the sick bay in the emergency department. His blood pressure is 70/palp, heart rate is 145 beats/min, oxygen saturation is 85% on room air, and he is breathing in excess of 40 times per minute. He is speaking in two- to three-word phrases only and appears pale and in distress. Auscultation reveals diminished breath sounds on the right. An emergent chest radiograph shows a dense opacity in the right lung. All of the following therapeutic steps are appropriate to consider for Mr. Boyle EXCEPT:

A. Bronchoscopic examination of the airways and consideration of bronchoscopically directed cauterization or laser therapy
B. Consultation with the interventional radiology team to evaluate for bronchial artery angiography and potential embolization
C. Endotracheal intubation with a dual-lumen endotracheal tube and mechanical ventilation
D. Placement of the patient in the left lateral decubitus position
E. Placement of two large-bore peripheral IV catheters and aggressive administration of IV crystalloids

I-99. A patient is evaluated in the emergency department for cyanosis. On exam, you note that the skin and mucous membranes are both affected. Which of the following is the most likely cause?

A. Cold exposure
B. Deep vein thrombosis
C. Hereditary hemorrhagic telangiectasia
D. Raynaud phenomenon
E. Thrombophlebitis

I-100. You are reading a fascinating historical account of human experiments done in the mid-to-early 20th century to discover the physiologic effects of hypoxia. In these experiments, men reside in a large compression chamber for 1 month. The scientists then slowly reduce the oxygen content in the room's air by 0.5% per day until they reach a level where the men have a resting hemoglobin oxygen saturation of 87%. The men then reside in this state for 2 weeks. While you question the ethical considerations involved, you also think of the physiologic changes in the men residing in the compression chamber. You know that these men are likely to experience all of the following EXCEPT:

A. Dilation of systemic arterioles
B. Elevated expression of hypoxia-induced factor 1
C. Elevated expression of vascular endothelial growth factor
D. Decreased right ventricular afterload
E. Systemic venoconstriction

I-101. Each of the following five 50-year-old women has an arterial PaO_2 of 60 mmHg. Which of them will have the highest arterial hemoglobin oxygen saturation?

A. A healthy woman standing on the top of a 3000-m peak in the Peruvian Andes
B. A woman with end-stage chronic obstructive pulmonary disease due to α_1 antitrypsin deficiency
C. A woman obtunded from an overdose of morphine
D. A woman found by paramedics after attempting suicide by placing a plastic bag over her head
E. A woman with severe neuromuscular weakness due to myasthenia gravis

I-102. Each of the following patients has the same skin tone, an identical cardiac output, and an identical arterial hemoglobin oxygen saturation of 80%. Which patient will likely appear most cyanotic?

A. A man with a gastrointestinal bleed from an esophageal varix and a hemoglobin of 8 g/dL
B. A normal, healthy man exultant after just having summited a 4000-m peak in Tibet for the first time
C. A man with long-standing congenital heart disease due to uncorrected tetralogy of Fallot and a hemoglobin of 20 g/dL
D. A previously healthy man with bacterial pneumonia
E. A previously healthy man with a large pulmonary embolism

I-103. Ms. Copell is a 39-year-old professional dancer who comes to see you to ask you about the need for antibiotics before going to the dentist's office. She reports being told she has a heart murmur and thinks it was mitral valve prolapse (MVP). She has no prior history of rheumatic fever or connective tissue disease. If she has MVP, which of the following should you expect to hear on cardiac auscultation?

A. Late diastolic murmur over the sternum
B. Late systolic murmur at the apex
C. Mid-diastolic murmur at the apex
D. Pansystolic murmur at the left upper sternal border
E. Pansystolic murmur at the right sternal border

I-104. Mr. Carpentier presents to the emergency room with 2 weeks of fever and 30 minutes of acute, overwhelming shortness of breath. His heart rate on presentation is 120 beats/min, blood pressure is 90/75, and oxygen saturation is 84% on room air. Examination reveals diffuse pulmonary rales, and chest x-ray confirms pulmonary edema. After auscultation of his precordium, you suspect that he has acute mitral regurgitation (MR). Compared with the murmur of chronic MR, the murmur you heard:

A. Is crescendo-decrescendo in pattern
B. Is holosystolic and proceeding to obscure S_2
C. Is likely louder and associated with a thrill
D. Is shorter, ending in early diastole and decrescendo in shape
E. Will likely be easily appreciated with the bell of the stethoscope off the chest

I-105. Mr. Abraham is a 62-year-old former sea urchin collector with a history of right total knee replacement 10 years ago and prior tobacco abuse. He presents to your office complaining of chest pain with moderate exertion and some mild dyspnea with walking up hills. On examination, you note a mid-systolic murmur. After careful listening, you are unsure whether this is the murmur of aortic stenosis or of the obstructive form of hypertrophic cardiomyopathy (HCM). Which maneuver is appropriately matched to the clinical finding that would suggest that this murmur is due to obstructive HCM as opposed to aortic valvular stenosis?

A. Handgrip maneuver: diminished intensity of the murmur
B. Initiating milrinone intravenously: augmentation of the systolic murmur
C. Palpation of the carotid impulse: a diminished, delayed carotid upstroke
D. Stand to squat: augmentation of the intensity of the murmur
E. Valsalva maneuver: augmentation of the intensity of the murmur

I-106. A 42-year-old man with known Marfan syndrome presents to your office for his yearly follow-up. His heart rate is 85 beats/min, and blood pressure is 140/55. His carotid pulses are bounding. On auscultation, you identify an early diastolic, blowing decrescendo murmur at the right second interspace, radiating to the right sternal border. Curiously, you also hear a lower pitched mid-to-late grade 2 diastolic murmur at the apex. Although you are fairly certain the first murmur is from aortic regurgitation and are concerned about aortic root disease, you are not certain whether the latter murmur is due to the Austin Flint phenomenon (turbulence at the mitral inflow area from admixing of the regurgitant aortic flow and forward mitral flow) or from structural mitral valve stenosis. Unfortunately, your echocardiogram machine is broken. Which maneuver listed below is appropriately matched to the finding of the apical murmur that would convince you that this murmur is due to the Austin Flint phenomenon and not mitral stenosis (MS)?

A. Administration of phenylephrine: decreased murmur intensity.
B. Administration of immediate-release nifedipine: increased murmur intensity.
C. Amyl nitrate administration: increased murmur intensity.
D. Handgrip: increased murmur intensity.
E. The murmur of valvular MS and the Austin Flint murmur will respond identically to every maneuver.

I-107. Mrs. Edwards is a 37-year-old sushi chef, originally from the Izu Islands of Japan, with a history of rheumatic fever, continuous atrial fibrillation, and known mitral stenosis. She feels well at rest but is limited by dyspnea to mild exertional efforts only. She has stopped biking to the market to pick out the fresh fish daily, delegating these responsibilities to her son. On auscultation of Mrs. Edward's precordium, you expect to hear all of the following findings EXCEPT:

A. A loud S_1
B. A high-pitched sound occurring shortly after S_2
C. A mid-diastolic, low-pitched decrescendo murmur
D. An increase in the murmur just before systole
E. Augmentation of the murmur intensity with turning the patient in the left lateral decubitus position

I-108. Mr. Garibolldy, a 58-year-old former professional badminton champion, presents to your clinic for evaluation of palpitations. Unfortunately, since his badminton career ended 25 years ago, he has not kept up his physical fitness. As his primary care provider, you have been trying to manage his hypertension, hyperlipidemia, tobacco abuse, and lack of physical exercise. Two weeks ago, he decided to take your advice and start jogging to increase his aerobic exercise. However, at your clinic visit with him today, he notes that every time he starts to jog, he senses a rapid heart rate with fluttering in his chest, feels very short of breath, and feels like he is going to pass out. Once, he thinks he may have lost consciousness briefly after sitting at the side of the jogging track. These sensations last for several minutes after he stops to rest. What is the most appropriate response to this patient?

A. Palpitations may be caused by electrical disturbances but also can be caused by valvular disease or other vascular diseases.
B. "Perhaps you should try swimming, jogging is an intense orthostatic challenge for the physically unfit."
C. Since the palpitations are infrequent, a 24-hour Holter monitor is the best way to diagnose the cause of these symptoms.
D. "This is probably just in your head" because most common causes are psychiatric.
E. This is worrisome because most arrhythmias are associated with palpitations.

I-109. Mr. Land is a 67-year-old man who was admitted to the hospital due to fatigue and fevers at home. On presentation, he is febrile and short of breath with crackles on examination in the right lower lobe. On imaging he has consolidations in the right greater than left lower lobes with possible debris in the right main-stem bronchus. While conducting your history and physical during dinner time, you notice that when he eats something he tries to keep the food in his mouth for a long period of time and frequently drools or has spillage of food. You also note frequent coughing that was not present when he is not eating. Which of the following is the next most appropriate test to determine the degree of swallowing dysfunction?

A. Barium radiography
B. CT of the chest
C. Esophageal manometry
D. Fluoroscopic swallow study
E. Upper endoscopy with biopsy

I-110. A 77-year-old woman seeks your opinion because she has lost weight over the last 9 months. She reports her weight has fallen from 165 to 140 lb without any effort on her part to lose weight. She had a hip fracture after a fall 3 months ago that was successfully surgically repaired. She reports that her mobility is good. There are no fevers or night sweats. Her review of systems is otherwise negative, and she reports an intact but not voracious appetite. Medications include warfarin with a well-controlled international normalized ratio. She is a lifelong nonsmoker and has one glass of wine less than twice per week. Which of the following is true regarding her weight loss?

A. Fifteen pounds in 9 months is not a significant amount of weight loss, nothing to worry about.
B. Appropriate testing for this patient would include laboratory testing, basic imaging, and depression and dementia screening.
C. This is quite abnormal for someone in their 70s as healthy aging people tend to continually gain weight.
D. Although weight loss can be noticeable and worrisome, it is not associated with an increased risk of mortality.
E. With appropriate testing, a cause of weight loss is nearly always found.

I-111. Peptic ulcers are the most common cause of upper gastrointestinal bleeding (UGIB), accounting for approximately 50% of UGIB hospitalizations. Which of the following treatment recommendations regarding peptic ulcer disease is correct?

A. Constant-infusion proton pump inhibitor (PPI) is superior to intermittent PPIs to prevent bleeding in patients with high-risk ulcers.
B. *Helicobacter pylori* treatment is not recommended for the prevention of bleeding peptic ulcers.
C. If nonsteroidal anti-inflammatory drugs must be given in a patient with peptic ulcer disease, a PPI is also recommended.
D. Patients who are taking aspirin for secondary prevention of heart disease should wait 2–3 weeks after UGIB episode to restart aspirin.
E. Patients with bleeding ulcers unrelated to infection or medications should remain on a PPI for 3 months.

I-112. A 33-year-old man is referred to the emergency department after his colleagues told him they were worried about the yellowing of his skin that they have noticed recently. He denies any new symptoms or physical ailments. He is healthy, exercises regularly, and follows a strict vegan diet. His past medical history is unremarkable and he takes no medications. On further examination, which of the following findings is reassuring that this is not a serious problem?

A. Associated dark urine
B. Scleral icterus
C. Skin discoloration limited to the palms and soles
D. Uniformly distributed skin discoloration

I-113. A 56-year-old woman with an unknown past medical history presents to the hospital with abdominal swelling. Physical examination suggests ascites, and abdominal ultrasound confirms a large volume of intraperitoneal fluid, the absence of hepatic vein thrombus, and no identifiable liver masses. You perform a paracentesis, removing 4 L of serous fluid from the abdomen. Below are the laboratory results from the patient's serum and ascites studies. Which of the following is the most likely diagnosis?

Serum	
Sodium	132
Creatinine	1.2
Albumin	3.2
Bilirubin	2.1
Ascites	
Albumin	2.6
Protein	0.9

A. Budd-Chiari syndrome
B. Cirrhosis
C. Heart failure
D. Peritoneal carcinomatosis
E. Veno-occlusive disease

I-114. Mr. Jeatir is a 42-year-old former baseball player who started chewing gum incessantly after stopping baseball (where his gum chewing used to be limited to only during games). Coinciding with this, he also notes an increase in abdominal swelling and belching. Which of the following is the most likely contributor?

A. Abdominal fat
B. Carbon dioxide
C. Hydrogen gas
D. Methane gas
E. Nitrogen gas

I-115. Mr. Gruakar is a 63-year-old man with abdominal swelling for the past few months. He has not been seen by a doctor in many years, but can no longer tolerate the swelling and presents for further management. Abdominal ultrasound confirms the presence of a large amount of ascites, without any masses noted. He undergoes abdominal paracentesis, which shows serum-ascites albumin gradient gap of 1.3 and ascitic protein of 1.0 g/dL. Which of the following is the best treatment option to control his ascites?

A. Multidrug antibiotic treatment
B. Referral to cardiology for presumed heart failure
C. Referral to nephrology for presumed nephrotic syndrome
D. Referral to oncology for further workup and treatment of presumed malignancy
E. Spironolactone and furosemide

I-116. Mr. Hershort presents with the complaint of abdominal swelling. For the past month, he has noticed that his abdomen has become increasingly large, and he has been forced to buy new pants with an increased waist size twice. He denies any change in bowel movements but does now feel shortness of breath when walking and lying down. On physical examination, his abdomen is distended, but soft and nontender. His abdomen is dull to percussion, and you detect a fluid wave in his abdomen on physical examination. Curiously, you detect pulsations with light palpation over his liver. His lungs are clear to auscultation. Cardiac palpation reveals a systolic heave just to the left of the sternum, and a holosystolic murmur and loud P_2 are appreciated on auscultation. He has a positive Kussmaul sign. You insert (under sterile conditions) into his internal jugular vein a fluid-filled catheter connected to a pressure manometer located at the level of the patient's heart when supine. You advance the catheter into various venous spaces, occasionally inflating a balloon just proximal to the catheter tip to "wedge" it into the vein or artery. Which of the following locations will yield a normal pressure?

A. Internal jugular vein
B. Right ventricle
C. Unwedged hepatic vein
D. Wedged hepatic vein
E. None of the above

I-117. Mr. Hattah is a 61-year-old man who presents to his primary care physician for a routine physical examination. He says he has been feeling well except for some intermittent generalized achiness. His only medications are lisinopril and atorvastatin. He has no abnormalities on his physical examination. His urine dipstick is positive for hematuria, without proteinuria. On urinalysis, there are no red blood cells seen on urine microscopy, with no proteinuria or pyuria. Which of the following most likely explains the discrepancy between the negative urine microscopy and the positive dipstick result?

A. Hypercalciuria is the principal contributor.
B. It was most likely a false-negative urine microscopy.
C. Statin-induced rhabdomyolysis causing myoglobinuria is present.
D. The patient likely has a urinary tract infection.
E. The patient only intermittently has hematuria at different times.

I-118. Mr. Spearoti is a 47-year-old long-haul truck driver with a history of mild chronic kidney disease (baseline creatinine 1.4 mg/dL) and hypertension. Recently, he was complaining of some shoulder pain exacerbated by his work. Further, at his primary care appointment, his blood pressure was elevated at 150/95. He was started on lisinopril 20 mg daily and advised to take naproxen 500 mg bid. Two weeks later, he presents to the emergency department with muscle cramps and is found to have a creatinine of 4.9 mg/dL. His blood pressure is 135/80. Renal ultrasound reveals no hydronephrosis and normal-appearing kidneys. His urinalysis is bland, and urine microscopy reveals hyaline casts. Urinary sodium is undetectable. Which of the following is the likely cause of his acute renal failure?

A. Acute interstitial nephritis
B. Acute tubular necrosis
C. Glomerulonephritis
D. Glomerular vasomotor dysfunction
E. Obstructive uropathy

I-119. A 58-year-old man spent the past month camping in the woods alone while on a spiritual journey of self-isolation. After 1 month, he returned because of hip pain after a fall. Before going home, he decided to go to the emergency room for x-rays. On physical examination his vital signs were within normal limits. He had long hair and a long beard and appeared in no acute distress. His neurologic examination was normal. He had some right hip pain with active and passive motion. He had routine labs prior to imaging that was notable for a serum sodium (Na) of 126 mEq/dL, potassium (K) of 4.9, and creatinine (Cr) 1.0. He is given 2 L of normal saline over 4 hours. X-rays show no fractures. He is given recommendations for follow-up and pain control. He goes home and the next day he develops paraparesis so he calls 911 and is brought back to the emergency department. On examination he has 2/5 weakness of bilateral proximal and distal lower extremities. He is also having some speech difficulties. His basic metabolic panel is within normal: Na 140 mEq/dL, K 4.8, and Cr 0.9. Which is the anatomic location of the lesion most likely contributing to his symptoms?

A. Cerebral motor cortex
B. Cervical spine
C. Lumbar nerve roots
D. Lumbar spine
E. Pons

I-120. For the patient described in question I-119, what is the next best step in diagnosis or management?

A. Broad-spectrum antibiotics
B. Lower his serum sodium
C. Lumbar puncture to look for albuminocytologic dissociation
D. High-dose steroids
E. Obtain an MRI of the lumbar spine

I-121. As part of an experiment, you infuse a nonmetabolized osmotically active solute into a peripheral vein of a subject, measuring serum osmolality at a distant vein every 2 minutes. When osmolality reaches about 285 mOsm/kg, you know that several physiologic changes will occur. These include all of the following EXCEPT:

A. Aquaporin-2 water channels will be actively inserted in the luminal membrane of the glomerular collecting duct.
B. Neurons in the hypothalamus will release arginine vasopressin into the circulation via the posterior pituitary.
C. The patient will feel thirsty.
D. The renal medullary osmotic gradient will decrease.
E. Urinary osmolality will rise.

I-122. A patient presents to you with 2 days of frequent vomiting. On examination, he has dry mucous membranes and diminished skin turgor. While supine, blood pressure and heart rate are 110/75 and 90 beats/min, respectively. When standing, blood pressure and heart rate are 85/55 and 110 beats/min, respectively. Serum pH is 7.45 with a bicarbonate level of 32 mEq/dL. You obtain a urine sample for testing. Which of the following do you expect to be true?

A. Urine specific gravity will be <1.020.
B. Urine chloride will be >25 mM.
C. Urine osmolality will be <300 mOsm/kg.
D. Urine sodium will be >20 mM.

I-123. Which of the following conditions is associated with hyponatremia *and* suppression of circulating antidiuretic hormone levels?

A. Central diabetes insipidus
B. Cirrhosis
C. Dehydration
D. Heart failure
E. Psychogenic polydipsia

I-124. You are called in to consult on the curious case of Mr. Atah. He is a 21-year-old man who was admitted with mild pancreatitis. A CT scan showed no gallstones, and he fervently denies any history of alcohol intake. Strangely, his serum sodium is measured by the core laboratory as between 117 and 121 mEq/dL on repeated tests, and prior reports faxed from his primary care clinic indicate that his serum sodium 1 year previously (in a state of normal health) was 121 mEq/dL. On examination, he has an arcus senilis and tendinous xanthomas. What is the likely cause of this patient's hyponatremia?

A. A mutation leading to a constitutively active V2 aquaporin protein in the nephron
B. Cirrhosis
C. Excess inappropriate activity of antidiuretic hormone
D. Polydipsia
E. Pseudohyponatremia

I-125. Mr. Matherli is a 54-year-old man with nephrogenic diabetes insipidus (NDI) from lithium therapy. Usually, he is excellent about keeping up his free water intake to control his sodium level. However, he was involved in a car accident requiring an operation at an outside hospital. There, they did not know about his NDI, and after being NPO for 48 hours, he was found to have a serum sodium of 160 mEq/dL. He is a 100-kg man. To correct his serum sodium over the next 24 hours, at what approximate rate should the physician run IV 5% dextrose in water (for free water)?

A. 50 mL/h
B. 100 mL/h
C. 150 mL/h
D. 250 mL/h
E. 350 mL/h

I-126. An 82-year-old man with a past medical history of stage 1 lung cancer that was resected 2 years ago with no residual disease comes to your primary care clinic because of nausea and poor appetite. Symptoms started about 1 month ago and have been pretty constant. On review of symptoms, he does endorse occasional back pain attributed to arthritis that has been worsening as well. There are no abnormalities on the physical exam. He is found to have an elevated serum calcium of 12.2 mg/dL. Additional laboratory studies are presented in the table below. Which of the following is the likely the cause of his symptoms?

Sodium	132 mEq/dL
Bicarbonate	26 mEq/dL
Total protein	5.1 g/dL
Albumin	2.5 g/dL
Parathyroid hormone level	<15 pg/mL (reference range: 15–65 pg/mL)
Parathyroid hormone related peptide	Undetectable
1,25-Dihydroxyvitamin D	Within normal

A. Bone metastases.
B. Granulomatous disease.
C. His corrected serum calcium is normal and not contributing to his symptoms.
D. Paraneoplastic process.
E. Primary hyperparathyroidism.

I-127. You refer the patient described in question I-126 to the emergency department for further management. On repeat labs his serum calcium is 11.5 and albumin is 2.5g/dL. Heart rate is 132, blood pressure 100/55, respiratory rate 18 breaths/min, and temperature 37.2°C (99°F). Which of the following is the next best step in management?

A. 80 mg IV furosemide.
B. Aggressive hydration with IV saline.
C. Hydrocortisone 100 mg daily.
D. No therapy is needed; corrected serum calcium is normal.
E. Zoledronic acid 4 mg IV.

I-128. A 66-year-old man presents to the urgent care center with vague complaints of nausea and decreased appetite over the last 4–6 weeks. Physical examination reveals normal vital signs and no abnormality other than a thin man with mild diffuse abdominal tenderness without guarding or rebound. The patient is found to have a reduced serum calcium of 7.8 mg/dL. He denies any musculoskeletal symptoms. Additional laboratory studies are presented in the following table:

Sodium	139 mEq/dL
Potassium	3.8 mg/dL
Bicarbonate	26 mEq/dL
Creatinine	1.2 mg/dL
Glucose	109 mg/dL
Total protein	6.2 g/dL
Albumin	2.0 g/dL
Bilirubin	1.2 mg/dL

For the patient's hypocalcemia, which of the following is the most appropriate response?

A. Administer calcium gluconate 1 g IV.
B. Check magnesium levels and replete if deficient.
C. Check vitamin D levels and replete if deficient.
D. No further response is necessary.
E. Prescribe oral calcium bicarbonate daily.

I-129. A 55-year-old man with a recent right-sided partial colectomy for stage 1 colon cancer comes back into the emergency room because of nausea and vomiting. Initial x-ray shows dilated loops of small bowel with air fluid levels. A nasogastric tube is placed and the following labs are obtained. Which of the following metabolic acid-base disorders does this patient have?

Sodium	145 mEq/L
Chloride	100 mEq/L
Glucose	130 mg/dL
HCO_3^-	32
Creatinine	2.8 (baseline 1.0)
Potassium	2.9 mEq/L
Arterial pH	7.50
$PaCO_2$	47 mmHg

A. Metabolic acidosis
B. Metabolic alkalosis
C. Respiratory acidosis
D. Respiratory alkalosis
E. Combined metabolic alkalosis and respiratory acidosis

I-130. John Rickerd is an 18-year-old man with a history of depression who presents to the emergency department after being found confused in his garage. He is noted to have a high anion gap metabolic acidosis, elevated creatinine, and rectangular coffin lid–appearing crystals in his urine on microscopic analysis. Arterial pH is 7.33. Measured serum osmolality is 320 mmol; serum sodium is 140, blood urea nitrogen is 28, and glucose is 180. Additional laboratory tests to identify etiology are pending. Which of the following is the next appropriate step?

A. Administer fomepizole
B. Administer IV bicarbonate
C. Await ethylene glycol level before initiating therapy
D. Initiate emergent renal dialysis

I-131. A 51-year-old man comes to your clinic because of progressive changes in skin color of his hands. A photo of his hands is shown in Figure I-131. Which of the following diagnostic techniques would confirm the diagnosis?

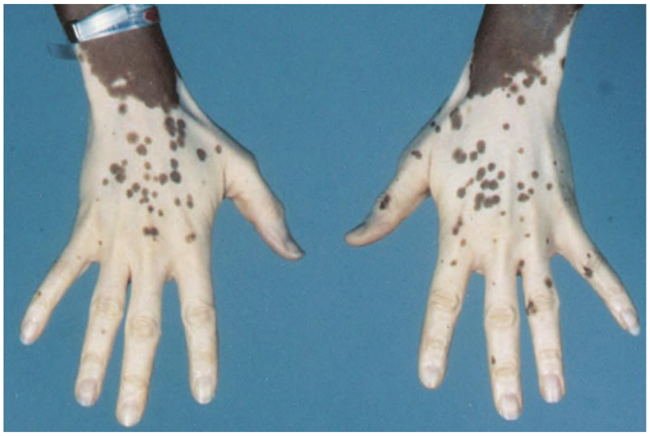


FIGURE I-131

A. Diascopy with brown-pink "apple jelly" appearance
B. KOH preparation showing pseudohyphae
C. Skin biopsy
D. Tzanck smear showing epithelial giant cells
E. Wood light showing totally white skin

I-132. Smallpox vaccinations were discontinued several decades ago for the general population. While some people may still get them (for example, certain military personnel), which of the following conditions is a contraindication to smallpox vaccination?

A. Age over 50 years
B. Chronic obstructive pulmonary disease
C. Early-stage Lung cancer
D. Eczema
E. Peripheral vascular disease

I-133. A 6-year-old boy is brought in by his mother complaining of approximately 6 months of itching and scaling of the skin inside the elbows (Figure I-133). The area gets red occasionally and improves with over-the-counter topical steroid creams. There are no fever, chills, night sweats, or red streaks ascending the arm. The family has a pet cat and lives in a clean apartment. All of the following statements concerning this child are true EXCEPT:

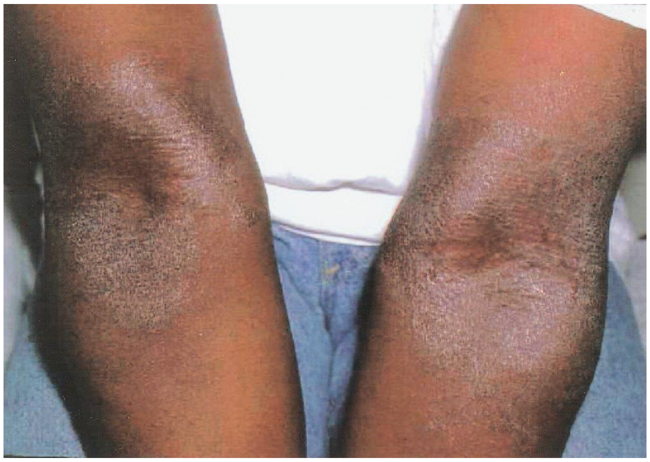


FIGURE I-133 Used with permission from Robert Swerlick, MD.

A. Both of his parents have a history of atopic dermatitis.
B. He likely has a history of asthma or atopic rhinitis.
C. His serum IgE levels are elevated.
D. He has a greater than 70% chance of spontaneous resolution.
E. His lesions will likely respond to topical tacrolimus.

I-134. A 42-year-old woman presents with new ulcers on her bilateral lower extremities. They started out as pustules but then turned into ulcers with necrotic violaceus edges and a peripheral erythematous halo. A picture of the lesion is shown in Figure I-134. She has never had lesions like this before. Her past medical history is notable only for ulcerative colitis and a deep vein thrombosis diagnosed 4 months ago for which she has been on warfarin since then. Which of the following is the most likely cause of her ulcers?

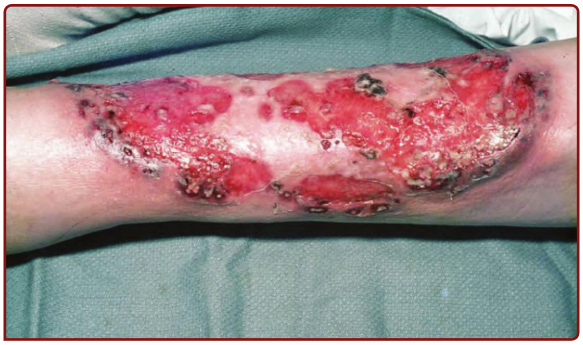


FIGURE I-134 Reproduced with permission from Kang S et al: *Fitzpatrick's Dermatology*, 9th ed. New York: McGraw Hill, 2019.

A. Cholesterol emboli
B. Erythema multiforme
C. Pyoderma gangrenosum
D. Squamous cell carcinoma
E. Warfarin-induced necrosis

I-135. A 45-year-old woman complains of hair loss. She states that whenever she brushes her hair she feels that there are excessive numbers of hairs that are shed, and she also notices the same phenomenon when she washes her hair. It has progressed to the point that she states her hair is noticeably thinner diffusely, and her hairdresser has commented on this as well. Approximately 5 months ago, she was hospitalized for acute gallstone pancreatitis with high fevers and underwent endoscopic retrograde cholangiopancreatography. This was followed by a laparoscopic cholecystectomy after 14 days. Overall, she was hospitalized for a total of 21 days. She has now returned to her baseline functional status. Her past medical history is significant for obesity, hyperlipidemia, and glucose intolerance. She is taking metformin 1000 mg daily and rosuvastatin 10 mg daily. On physical examination, she has only mild hair thinning. When a small area of the hair is pulled, more than 10 hairs are extracted at the root. There is no scaling or scarring on the scalp, and no broken hairs are seen. Which of the following do you recommend?

A. Observation only
B. Oral terbinafine
C. Psychotherapy
D. Topical minoxidil
E. Topical anthralin

I-136. A 29-year-old man presents to your clinic with skin lesions on his face, scalp, and around his ears as seen in Figure I-136. The lesions initially were erythematous papules with a thick, adherent scale that, when removed, its underside shows small excrescences that correlate with the openings of hair follicles. Which of the following would be expected on biopsy of one of these lesions?

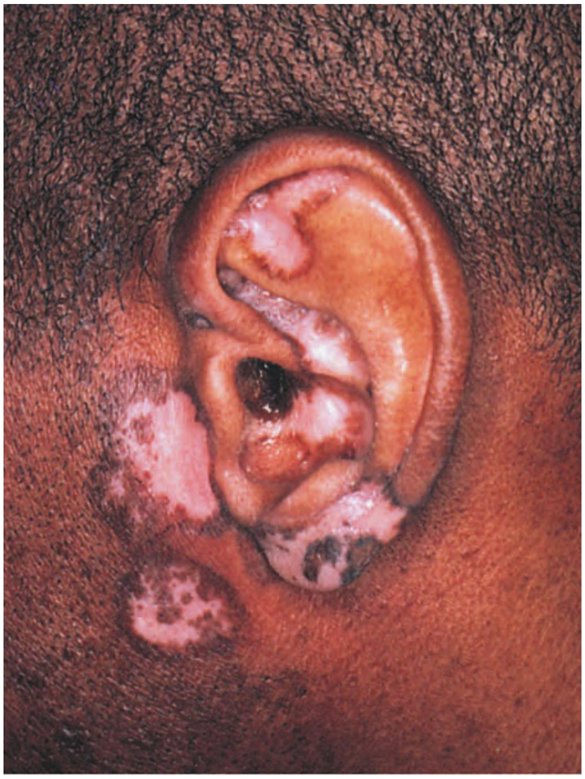


FIGURE I-136

A. Deposits of IgG on the surface of keratinocytes.
B. Direct immunofluorescence will most likely be normal.
C. Eosinophil-rich infiltrate at sites of vesicle formation and in perivascular areas.
D. Hyperkeratosis, follicular plugging, mononuclear cell infiltrate adjacent to the epidermal, adnexal, and microvascular basement membranes.
E. Intraepidermal vesicle formation secondary to loss of cohesion between epidermal cells.

I-137. A 73-year-old man develops pruritic blistering lesions on his lower abdomen, groin, and legs. The lesions begin with raised red itchy plaques and progress to tense bullae. After rupture, these lesions have largely healed without scarring except when excessively inflamed from excoriation. He has had no changes in his chronic medications for diabetes mellitus, gout, and benign prostatic hypertrophy. He was previously treated for renal cell carcinoma 15 years ago. An image of his rash is shown in Figure I-137. Which of the following is the most likely diagnosis?

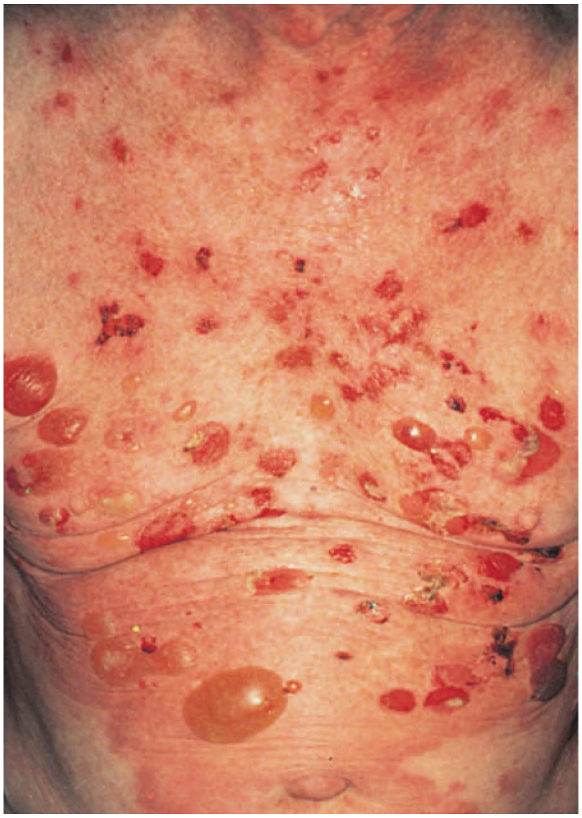


FIGURE I-137 Used with permission from Yale Resident's Slide Collection.

A. Bullous pemphigoid
B. Epidermolysis bullosa acquisita
C. Paraneoplastic pemphigus
D. Pemphigus vulgaris
E. Urticarial vasculitis

I-138. A 24-year-old woman seeks evaluation for a rash that is present diffusely on her back, buttocks, elbows, and knees. The rash began abruptly, and the patient is complaining of severe pruritus and burning associated with the rash. A biopsy of the rash demonstrates neutrophilic dermatitis within the dermal papillae, and immunofluorescence highlights granular deposition of IgA in the papillary dermis and along the epidermal basement membrane zone. Which of the following treatments do you recommend for this patient?

A. Dapsone 100 mg daily
B. Gluten-free diet
C. Prednisone 40 mg daily
D. A and B
E. All of the above

I-139. Which of the following types of rashes are the most common drug-induced skin reactions?

A. Diffuse morbilliform rash
B. Diffuse urticaria
C. Follicular pustular eruptions
D. Mucosal ulcers
E. Papular rash

I-140. All of the following laboratory tests are helpful in determining the cause of photosensitivity in a patient EXCEPT:

A. Antinuclear antibody
B. Anti-La
C. Anti-Ro
D. Plasma porphyrin
E. Vitamin D levels

I-141. Which of the following drugs is associated with a phototoxic reaction?

A. Diclofenac
B. Glipizide
C. Hydrochlorothiazide
D. Levofloxacin
E. Promethazine

I-142. A normal red blood cell is approximately the size of which of the following:

A. Eosinophils
B. Normal lymphocytes
C. Reactive lymphocytes
D. Neutrophils
E. Platelets

I-143. A 65-year-old man is being evaluated for anemia. You make note of the white blood cells seen in Figure I-143. What is a possible treatment for this patient?

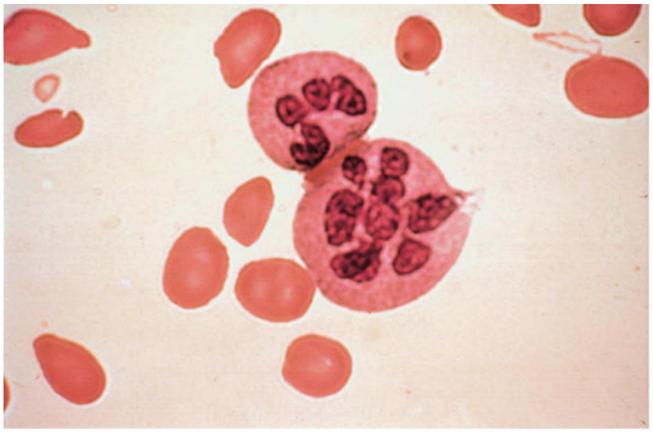


FIGURE I-143

A. Antibiotics, as this is a sign of bacterial sepsis
B. Chemotherapy, as this is a sign of acute myeloid leukemia
C. Chemotherapy, as this is a sign of chronic lymphoid leukemia
D. Vitamin B_{12}, as this is a sign of vitamin B_{12} deficiency
E. No additional treatment is needed, as these are normal white blood cells

I-144. A 36-year-old woman presents to your office complaining of easy fatigability. She reports a history of heavy menses and has been following a vegetarian diet. Her physical examination is normal with the exception of pale conjunctiva. Her labs are notable for a hemoglobin of 9.1 g/dL and hematocrit 27.6%. The mean corpuscular volume is 65 fL, mean corpuscular hemoglobin is 24 pg, and mean corpuscular hemoglobin concentration is 26%. The red cell distribution is 16.7%. A peripheral blood smear is shown in Figure I-144. Which of the following would you also expect to find?

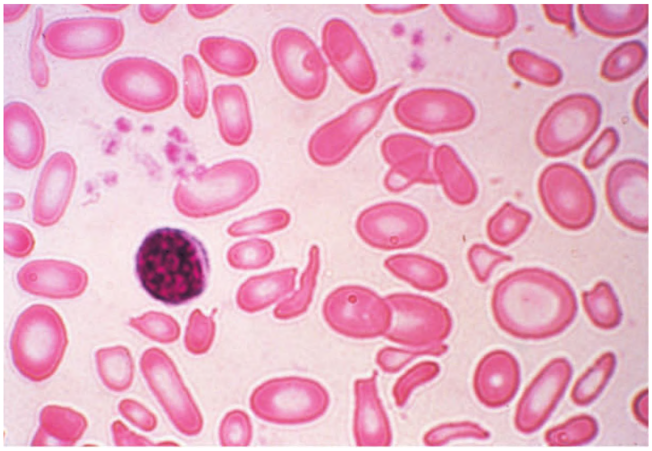


FIGURE I-144A Reproduced with permission from Hillman RS et al: *Hematology in Clinical Practice*, 5th ed. New York: McGraw Hill, 2010.

A. Erythropoietin levels would be decreased.
B. Hypoxia-inducible factor-1α would be decreased.
C. 2,3-Bisphosphoglycerate levels would be increased.
D. Reticulocyte count would be increased.

I-145. A 28-year-old woman presents to you for follow-up after a recent hospitalization for sickle cell pain crisis. She has had on average one hospitalization a month for pain crises over the last year. She also has a history of acute chest syndrome within the last year. On review of her labs just prior to discharge you note a hemoglobin of 9.8 g/dL, mean corpuscular volume 88 fL, and mean corpuscular hemoglobin concentration 30 pg. On review of her peripheral smear, in addition to seeing sickled red blood cells, what other characteristic finding would you expect?

A. Burr cells
B. Howell-Jolly bodies
C. Schistocytes
D. Spherocytes
E. Target cells

I-146. A 45-year-old male comes to your clinic with frequent headaches. Routine lab work is obtained and shows a hemoglobin of 18 g/dL. He reports smoking three packs per day for the past 20 years. You suspect this is the cause of his polycythemia. Which set of laboratory tests is consistent with that?

A. Elevated red blood cell mass, high serum erythropoietin levels, normal oxygen saturation
B. Elevated red blood cell mass, high serum erythropoietin levels, low arterial oxygen saturation
C. Elevated red blood cell mass, low serum erythropoietin levels, normal oxygen saturation
D. Elevated red blood cell mass, low serum erythropoietin levels, low arterial oxygen saturation

I-147. An 18-year-old comes to you for the first time after moving from a remote area with limited medical care. He has a history of multiple severe bacterial infections and albinism. A representative peripheral blood smear is shown in Figure I-147. What diagnosis is most consistent with this history and blood smear?

A. Acute myeloid leukemia
B. Chédiak-Higashi syndrome
C. Kostmann syndrome
D. Pelger-Hüet anomaly

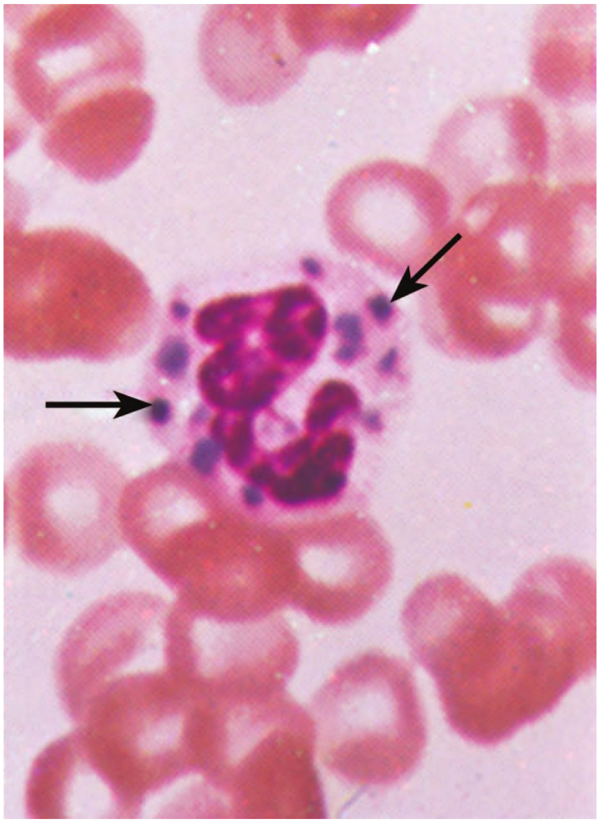


FIGURE I-147

I-148. A patient with long-standing HIV infection, alcoholism, and asthma is seen in the emergency room for 1–2 days of severe wheezing. He has not been taking any medicines for months. He is admitted to the hospital and treated with nebulized therapy and systemic glucocorticoids. His CD4 count is 8 and viral load is >750,000. His total white blood cell (WBC) count is 5200 cells/μL with 90% neutrophils. He is accepted into an inpatient substance abuse rehabilitation program and before discharge is started on opportunistic infection prophylaxis, bronchodilators, a prednisone taper over 2 weeks, ranitidine, and highly active antiretroviral therapy. The rehabilitation center pages you 2 weeks later; a routine laboratory check reveals a total WBC count of 900 cells/μL with 5% neutrophils. Which of the following new drugs would most likely explain this patient's neutropenia?

A. Darunavir
B. Efavirenz
C. Ranitidine
D. Prednisone
E. Trimethoprim-sulfamethoxazole

I-149. Which of the following is the most abundant receptor on a platelet and therefore a target for antiplatelet therapy?

A. Collagen
B. Glycoprotein IIb/IIIa
C. Protein C
D. Tissue factor
E. von Willebrand factor

I-150. You are consulted after an episode of postpartum hemorrhage in a 24-year-old woman. This was her first pregnancy, and she successfully delivered a healthy child at 39 weeks and 4 days. The child weighed 7 lb 12 oz, and the delivery was an uncomplicated spontaneous vaginal delivery. The uterine fundus contracted appropriately, but over the course of the next 12 hours, the patient had more than 1 L of bloody discharge. She has felt increasingly weak and has lightheadedness on standing. Her heart rate is 126 beats/min and blood pressure is 92/50. She appears pale. Her pulses are thready. Cardiovascular examination shows regular tachycardia. Her hemoglobin prior to delivery was 9.2 g/dL. It is now 6.0 g/dL. Her prothrombin time is 12.0, international normalized ratio is 1.1, and activated partial thromboplastin time is 42.5 seconds. On further questioning, the patient describes one other episode of prolonged oral bleeding in childhood at about age 7. At that time, she had a cap placed on a tooth and subsequently experienced significant bleeding. She bruises easily but has not had any episodes of hemarthrosis. She says she stopped playing soccer in grade school due to large bruises after minor injuries that were painful and embarrassing to her. She has had no other surgeries. She is taking iron supplements and prenatal vitamins. She has no allergies. She has a family history of excessive bleeding after a surgical procedure in her father from whom she is estranged. What do you suspect as the cause of the patient's illness?

A. Acquired inhibitor of coagulation
B. Factor VIII deficiency
C. Factor IX deficiency
D. Surreptitious ingestion of an anticoagulant
E. von Willebrand disease

I-151. A 68-year-old man is undergoing a total knee replacement for degenerative arthritis. His past medical history is significant for hypertension, diabetes mellitus, hyperlipidemia, gout, and obesity. His medication list includes metoprolol, sitagliptin, metformin, allopurinol, rosuvastatin, and aspirin daily. He is asked to stop his aspirin in preparation for surgery. Which of the following test(s) is/are indicated prior to surgery to ensure that the patient is not at increased risk of postoperative bleeding complications?

A. Activated partial thromboplastin time
B. Bleeding time
C. Prothrombin time
D. A and C
E. A, B, and C

I-152. A 62-year-old woman is evaluated in a hematology clinic after a second episode of deep vein thrombosis (DVT). Her first episode occurred at age 34 following a pregnancy, and this episode occurred following an automobile accident that resulted in a femur fracture. She has no family history of DVT or pulmonary embolism. She is requesting a workup for hypercoagulability. Her automobile accident was 2 months ago. She remains casted and underwent surgical intervention on her fracture 4 weeks prior. She remains on low-molecular-weight heparin. What do you advise at the current time?

A. Do nothing. No further testing is indicated.
B. Send factor V Leiden and prothrombin 20210.
C. Send protein C and S levels.
D. Send antithrombin III levels.
E. Have the patient return in 3–6 months for further testing.

I-153. In which of the following clinical situations resulting in splenomegaly is a diagnostic splenectomy indicated?

A. Chronic myelogenous leukemia
B. Passive congestion due to portal hypertension
C. Sickle cell anemia
D. Stage I Hodgkin lymphoma
E. Stage III Hodgkin lymphoma

I-154. All of the following are expected in patients who have had a splenectomy EXCEPT:

A. Anisocytosis bodies on peripheral smear
B. Howell-Jolly bodies on peripheral smear
C. Increased risk of bacterial infections
D. Increased risk of viral infections
E. Nucleated erythrocytes

I-155. A 24-year-old woman seeks evaluation from her primary care provider for a "swollen gland" on the right side of her neck. She first noticed it about 2 weeks ago and has felt fatigued with a sore throat and low-grade fevers throughout this time. On examination, there is a dominant 2-cm right posterior cervical lymph node that is rubbery and mobile. It is tender to palpation. In addition, there are also several 0.5- to 1-cm lymph nodes in the bilateral anterior and posterior cervical chains as well as the occipital area. All of the following findings favor a benign diagnosis in this patient EXCEPT:

A. Age <50
B. Multiple lymph node involvement
C. Presence of mobility on examination
D. Presence of tenderness to palpation
E. Size of dominant node ≥2 cm

I-156. The presence of Howell-Jolly bodies, Heinz bodies, basophilic stippling, and nucleated red blood cells in a patient with hairy cell leukemia prior to any treatment intervention implies which of the following?

A. Diffuse splenic infiltration by tumor
B. Disseminated intravascular coagulation
C. Hemolytic anemia
D. Pancytopenia
E. Transformation to acute leukemia

ANSWERS

I-1. **The answer is A.** *(Chap. 1)* A series of reports from the Institute of Medicine (now the National Academy of Medicine) called for an ambitious agenda to reduce medical error rates and improve patient safety by designing and implementing fundamental changes in health care systems. It is the responsibility of hospitals and health care organizations to develop systems to reduce risk and ensure patient safety. Medication errors can be reduced through the use of ordering systems that rely on electronic processes or, when electronic options are not available, that eliminate misreading of handwriting. Whatever the clinical situation, it is the physician's responsibility to use powerful therapeutic measures wisely, with due regard for their beneficial actions, potential dangers, and cost. Implementation of infection control systems, enforcement of handwashing protocols, and careful oversight of antibiotic use can minimize the complications of nosocomial infections. Central-line infection rates have been dramatically reduced at many centers by careful adherence of trained personnel to standardized protocols for introducing and maintaining central lines. Rates of surgical infection and wrong-site surgery can likewise be reduced by the use of standardized protocols and checklists. Falls by patients can be minimized by judicious use of sedatives and appropriate assistance with bed-to-chair and bed-to-bathroom transitions. Taken together, these and other measures are saving thousands of lives each year.

I-2. **The answer is E.** *(Chap. 1)* Practice guidelines have been developed by many professional organizations and agencies as a decision-making aid to caregivers. Most organizations attempt to incorporate the most recent available evidence and concerns of cost-effectiveness into their guideline formulations. Despite increasing levels of nuance in current guidelines, they cannot be expected to account for the uniqueness of each individual and his or her illness. Furthermore, many discrepancies exist in guidelines from major organizations. By setting a standard of reasonable care in most cases, clinical guidelines provide protection to both clinicians (from inappropriate charges of malpractice) and to patients, particularly those with inadequate health care resources. Even though guidelines do provide this protection, they do not provide a rigid legal constraint for the conscientious physician. The physician's challenge is to incorporate the useful recommendations provided by the experts in guidelines and incorporate them into the care of each individual patient.

I-3. **The answer is D.** *(Chap. 1)* The field of molecular medicine is seeing rapid progress in fields other than genetics, bringing a new era of "-omics." *Metagenomics* is the genomic study of environmental species that have the potential to influence human biology directly or indirectly. *Metabolomics* is the study of the range of metabolites in cells or organs and ways in which they are altered in disease states. *Microbiomics* is the study of the resident microbes in humans and other mammals. Thermophiles do not reside in humans or other mammals by definition, thus, their study would not be included in the field of microbiomics. This field has proven particularly rich; the microbes residing on and in the human body comprise over 3–4 million genes (vs the 20,000 genes in the human haploid genome). *Proteomics* is the study of the library of proteins made in a cell or organ (including posttranslational modifications) and its complex relationship to disease. *Exposomics* is the study cataloguing environmental exposures and their impact on health and disease.

I-4. **The answer is D.** *(Chap. 1)* Evidence-based medicine (EBM) is an important cornerstone to the effective and efficient practice of medicine. EBM refers to the concept that clinical decisions should be supported by data with the strongest evidence gleaned from randomized controlled clinical trials. In many situations, data from observational studies such as cohort or case-control studies supply important information and contribute to the evidence used in clinical decisions in EBM. EBM is used by professional organizations and other agencies to formulate clinical practice guidelines, which are support tools to aid clinical decision-making (option C). Systematic reviews summarize the accumulated data from all existing clinical trials (option A). Comparative effectiveness research (option B) compares different approaches to treating disease to determine effectiveness from a clinical and cost-effectiveness standpoint. Anecdotal evidence (option E) is the weakest type of evidence, represents one individual's clinical experience, and is subject to the bias inherent in one practitioner's personal experience.

I-5. **The answer is B.** *(Chap. 2) Primordial prevention* is a more recent concept (first introduced in 1979) that focuses on prevention of the development of *risk factors* for disease, not just prevention of disease. Primordial prevention strategies emphasize upstream determinants of risk for chronic diseases, such as eating patterns, physical activity, and environmental and social determinants of health. It therefore encompasses medical treatment strategies for individuals as well as a strong reliance on public health and social policy. *Primary prevention* attempts to reduce the risk of incident disease among individuals with a risk factor. *Secondary prevention* strategies focus on avoiding the recurrence of disease and death in an individual who is already affected. For example, tamoxifen is recommended for women with surgically treated early-stage, estrogen-receptor-positive breast cancer, because it reduces the risk of recurrent breast cancer (including in the contralateral breast) and death. *Tertiary prevention* requires rapid action to prevent imminent death in the setting of acute illness, such as through percutaneous coronary intervention in the setting of ST-segment elevation myocardial infarction.

I-6. **The answer is A.** *(Chap. 4)* Abdominal ultrasound is only recommended for men age 65–75 with a history of smoking. Cholesterol testing is recommended for all men and women age 40–75, irrespective of body mass index or other risk factors. Dual-energy x-ray absorptiometry scans are recommended for women over the age of 65 without any risk factors and for women 60–65 who do have risk factors for osteoporosis. Mammograms are recommended for women age 50–75, irrespective of risk factors as shown in Table I-6.

TABLE I-6 **Screening Tests Recommended by the U.S. Preventive Services Task Force for Average-Risk Adults**

Disease	Test	Population	Frequency	Chapter
Abdominal aortic aneurysm	Ultrasound	Men 65–75 who have ever smoked	Once	—
Alcohol misuse	Alcohol Use Disorders Identification Test	All adults	Unknown	445
Breast cancer	Mammography with or without clinical breast examination	Women 50–75	Every 2 years	—
Cervical cancer	Pap smear	Women 21–65	Every 3 years	66
—	Pap smear and HPV testing	Women 30–65	Every 5 years if HPV negative	—
Chlamydia/gonorrhea	Nucleic acid amplification test on urine or cervical swab	Sexually active women <25	Unknown	184
Colorectal cancer	Fecal occult blood testing	50–75	Every year	66, 77
—	Sigmoidoscopy	50–75	Every 5 years	—
—	Colonoscopy (or occult blood testing combined with sigmoidoscopy)	50–75	Every 10 years	—
Depression	Screening questions	All adults	Periodically	—
Diabetes	Fasting blood glucose or HgbA1c	Adults overweight, obese, or with hypertension	Every 3 years	396
Hepatitis C	Anti-HCV antibody followed by confirmatory PCR	Adults born between 1945 and 1965	Once	—
HIV	Reactive immunoassay or rapid HIV followed by confirmatory test	15–65	At least once	—
Hyperlipidemia	Cholesterol	40–75	Unknown	400
Hypertension	Blood pressure	All adults	Periodically	271
Intimate partner violence	Screening questions	Women of childbearing age	Unknown	—
Obesity	Body mass index	All adults	Unknown	—
Osteoporosis	DEXA	Women >65 or >60 with risk factors	Unknown	404

Abbreviations: DEXA, dual-energy x-ray absorptiometry; HCV, hepatitis C virus; HPV, human papillomavirus; PCR, polymerase chain reaction.

Source: Data from the U.S. Preventive Services Task Force 2017. Available from www.uspreventiveservicestaskforce.org/Page/Name/uspstf-a-and-b-recommendations/. Accessed December 9, 2020.

I-7. **The answer is B.** *(Chap. 4)* The human papillomavirus vaccine approval was expanded to include adults up to the age of 45 but does not include those over the age of 65. Herpes zoster vaccine is recommended in men and women over the age of 60. Pneumococcal vaccine is recommended in those over the age of 64 years. Tetanus-diphtheria and influenza vaccine are recommended in those over the age of 18. Influenza vaccine should be given yearly and tetanus-diphtheria every 10 years (Table I-7).

TABLE I-7 Preventive Interventions Recommended for Average-Risk Adults

Intervention	Disease	Population	Frequency	Chapter
Adult immunization	—	—	—	118, 119
Tetanus-diphtheria	—	>18	Every 10 years	—
Varicella	—	Susceptibles only, >18	Two doses	—
Measles-mumps-rubella	—	Women, childbearing age	One dose	—
Pneumococcal	—	>64	13 followed by 23 valent	—
Influenza	—	>18	Yearly	—
Human papillomavirus	—	Up to age 27	If not done prior	—
Zoster	—	>60	Once	—
Chemoprevention				
Aspirin	Cardiovascular disease	Aged 50–59 years with a ≥10% 10-year CVD risk	—	—
Folic acid	Neural tube defects in baby	Women planning or capable of pregnancy	—	—
Tamoxifen/raloxifene	Breast cancer	Women at high risk for breast cancer	—	—
Vitamin D	Fracture/falls	>64 at increased risk for falls	—	—

Abbreviations: CVD, cardiovascular disease.

I-8. **The answer is D.** (*Chap. 4)* The number of subjects needed to screen to prevent disease or death in one individual is the inverse of the absolute difference in mortality. In this example, a 10% decrease in the 30% mortality reduces the absolute mortality to 27%. Therefore, the absolute difference in mortality is 3% (30% baseline – 27% postscreening), or 0.03. The number of screened subjects to prevent one death is 1.0/0.03 = 33.

I-9. **The answer is B.** *(Chap. 4)* Screening is indeed most effective when applied to relatively common diseases within the population. Because no test is perfect and posttest probability depends heavily on the disease prevalence within the population studied (pretest probability) by Bayes rule, any screening test will perform poorly if employed in the wrong population. To use an extreme example, screening for prostate cancer in men with prostate-specific antigen testing can only lead to an unacceptable level of false-positive results. On the other hand, populations with very high risk of the disease should undergo more rigorous screening and prevention measures. Patients with the *BRCA1* or *BRCA2* mutations have a very high lifetime risk of breast cancer. Thus, their chance of experiencing a false-negative result with traditional screening methods is unacceptable. It is recommended that these patients undergo breast MRI for screening (option E). This is not necessary in the general population, as their baseline risk of breast cancer is lower. In general, the presence of a latent period (asymptomatic presence of the disease) is a necessity for successful screening. If a disease has no latent period, screening becomes less effective as early treatment and prevention are obviated (option C). When considering the effectiveness of any screening method, disease incidence and overall mortality are the most important outcomes (option D). Comparing length of disease survival will be susceptible to lead and length time biases. Lead time bias occurs because screening identifies a case before it would have presented clinically, creating the perception that a patient lived longer after diagnosis simply by moving the date of diagnosis earlier rather than the date of death later. Length time bias occurs because screening is more likely to identify slowly progressive disease than rapidly progressive disease. Thus, within a fixed period of time, a screened population will have a greater proportion of these slowly progressive cases and will appear to have better disease survival than an unscreened population. It is also important to remember that every detected and treated disease by any screening mechanism does not necessarily represent a reduction in mortality (option A). Certain diseases have a long enough latent period that many patients die *with* the disease and not *from* the disease. In fact, recent estimates suggest that as many as 15–25% of breast cancers identified by mammography screening would never have presented clinically.

I-10. **The answer is A.** *(Chap. 4)* The National Heart, Lung, and Blood Institute found that low-dose chest CT scanning can detect tumors earlier, and CT was recently demonstrated to reduce lung cancer mortality by 20% in individuals aged 55–80 with at least a 30-pack-year history of smoking (*N Engl J Med.* 2011 Aug 4; 365(5): 395–409). This represented somewhat of a paradigm shift in how lung cancer screening was viewed. Historically, lung cancer screening in even high-risk populations had proven largely unsuccessful as many detected cancers were incurable at the time of detection by screening. A screening test is hardly ever a “no brainer.” In the case of lung cancer screening, several risks need to be discussed with the patient prior to referral for low-dose CT scanning. First, there is the risk of detection of an incurable cancer as discussed in question I-9. Second, even low-dose CT scanning exposes the patient to radiation and may increase their risk for subsequent neoplasm. Finally, every screening test carries a risk of a false positive. In the case of lung cancer screening, false-positive results may lead to invasive biopsies and even drastic surgeries such as pneumonectomy. Finally, although the sensitivity and specificity of a test do not depend on the population risk (a patient’s pretest probability), the posttest probability of disease provided by a positive or negative test does strongly depend on the pretest probability. This is why carefully choosing the appropriate risk patient for each screening test is important.

I-11. **The answer is B.** *(Chap. 4)* Predicted increases in life expectancy are average numbers that apply to populations, not individuals. Because we often do not understand the true nature of the risk of disease, screening and lifestyle interventions usually benefit a small proportion of the total population. For screening tests, false positives may also increase the risk of diagnostic tests. While Pap smears increase life expectancy overall by only 2–3 months, for the individual at risk of cervical cancer, Pap smear screening may add many years to life. The average life expectancy increases resulting from mammography (1 month), prostate-specific antigen (2 weeks), or exercise (1–2 years) are less than from quitting smoking (3–5 years).

I-12. **The answer is E.** *(Chap. 6)* Many factors ubiquitous in health care systems can increase the likelihood of errors, including fatigue, stress, interruptions, complexity, and transitions. A recent study of house officers in the intensive care unit demonstrated that they were about one-third more likely to make errors when they were on a 24-hour shift than when they were on a schedule that allowed them to sleep 8 hours the previous night. High levels of stress and heavy workloads also can increase error rates. Thus, in extremely high-pressure situations, such as cardiac arrests, errors are more likely to occur. Strategies such as using protocols in these settings can be helpful, as can simple recognition that the situation is stressful. Interruptions also increase the likelihood of error and occur frequently in health care delivery. It is common to forget to complete an action when one is interrupted partway through it. Approaches that may be helpful in this area include minimizing interruptions and setting up tools that help define the urgency of an interruption. Complexity represents a key issue that contributes to errors. Providers are confronted by streams of data (e.g., laboratory tests and vital signs), many of which provide little useful information but some of which are important and require action or suggest a specific diagnosis. Tools that emphasize specific abnormalities or combinations of abnormalities may be helpful in this area. Transitions between providers and settings are also common in health care, especially with the advent of the 80-hour workweek, and generally represent points of vulnerability. Tools that provide structure in exchanging information—for example, when transferring care between providers—may be helpful.

I-13. **The answer is C.** *(Chap. 7)* Racial and ethnic disparities in health care exist and, because they are associated with worse health outcomes, are unacceptable. Racial and ethnic disparities in health care occur in the context of (1) broader historic and contemporary social and economic inequality and (2) evidence of persistent racial and ethnic discrimination in many sectors of American life. Many sources—including health systems, health care providers, patients, and utilization managers—may contribute to racial and ethnic disparities in health care. A small number of studies suggest that minority patients may be more likely to refuse treatments, yet these refusal rates are generally small and do not fully explain health care disparities. To provide recommendations regarding interventions aimed at eliminating health care disparities, the Institute of Medicine studied health system, provider, and patient factors. The study identified a set of root causes that included the following:

- Health system factors—These include issues related to the complexity of the health care system, the difficulty that minority patients may have in navigating this complex system, and the lack of availability of interpreter services to assist patients with limited English proficiency. In addition, health care systems are generally ill prepared to identify and address disparities.
- Provider-level factors—These include issues related to the health care provider, including stereotyping, the impact of race/ethnicity on clinical decision-making, and clinical uncertainty due to poor communication.
- Patient-level factors—These include patients' mistrust of the health care system leading to refusal of services, poor adherence to treatment, and delay in seeking care.

I-14. **The answer is A.** *(Chap. 8)* Many patients are not able to make informed decisions because of unconsciousness, dementia, delirium, or other medical conditions. Although only courts have the legal authority to determine that a patient is legally incompetent, in practice, physicians determine when patients lack the capacity to make particular health care decisions and arrange for authorized surrogates to make decisions for them, without involving the courts. Patients with decision-making capacity can express a choice and appreciate their medical situation; the nature of proposed care alternatives; and the risks, benefits, and consequences of each alternative. Patient choices should be consistent with their values and not the result of delusions or hallucinations. Physicians should use available assessment tools, other resources such as psychiatry consultation, and clinical judgment to ascertain whether individuals have the capacity to consent and make decisions for themselves. It should not be automatically assumed that a patient who disagrees with a recommendation or refuses treatment lacks capacity, but such decisions should be probed to be sure the patient has the capacity for an informed decision and that there are no misunderstandings. Simply being oriented to person, place, and time is not adequate to ensure capacity.

I-15. **The answer is D.** *(Chap. 9)* Fundamental to ensuring quality palliative and end-of-life care is a focus on four broad domains: (1) physical symptoms; (2) psychological symptoms; (3) social needs that include interpersonal relationships, caregiving, and economic concerns; and (4) existential or spiritual needs. Although patients may or may not be receiving treatment, the focus of palliative care and hospice is not on the primary treatment of the underlying disease.

I-16. **The answer is C.** *(Chap. 9)* Constipation is reported in up to 70–100% of patients requiring palliative care. Although hypercalcemia and other factors can cause constipation, it is most frequently a predictable consequence of the use of opioids for pain and dyspnea relief, and of the anticholinergic effects of tricyclic antidepressants, as well as due to the inactivity and poor diet common among seriously ill patients. If left untreated, constipation can cause substantial pain and vomiting and is associated with confusion and delirium. Whenever opioids and other medications known to cause constipation are used, preemptive treatment for constipation should be instituted. Although physical activity, adequate hydration, and dietary treatments with fiber can be helpful, each is limited in its effectiveness for most seriously ill patients, and fiber may exacerbate problems in the setting of dehydration or if impaired motility is the etiology. Fiber is contraindicated in the presence of opioid use. Stimulant and osmotic laxatives, stool softeners, fluids, and enemas are the mainstays of therapy (Table I-16).

TABLE I-16 Medications for the Management of Constipation

Intervention	Dose	Comment
Stimulant laxatives	—	These agents directly stimulate peristalsis and may reduce colonic absorption of water
Prune juice	120–240 mL/d	Work in 6–12 h
Senna (Senokot)	2–8 tablets PO bid	—
Bisacodyl	5–15 mg/d PO, PR	—
Osmotic laxatives	—	These agents are not absorbed. They attract and retain water in the gastrointestinal tract
Lactulose	15–30 mL PO q4–8h	Lactulose may cause flatulence and bloating
Magnesium hydroxide (Milk of Magnesia)	15–30 mL/d PO	Lactulose works in 1 day, magnesium products in 6 h
Magnesium citrate	125–250 mL/d PO	—
Stool softeners	—	These agents work by increasing water secretion and as detergents, increasing water penetration into the stool
Sodium docusate (Colace)	300–600 mg/d PO	Work in 1–3 days
Calcium docusate	300–600 mg/d PO	—
Suppositories and enemas	—	—
Bisacodyl	10–15 PR qd	—
Sodium phosphate enema	PR qd	Fixed dose, 4.5 oz, Fleet's

Abbreviations: PR, per rectum.

I-17. **The answer is C.** *(Chap. 9)* Advance care planning documentation is an increasing component of medical practice. As of 2006, 48 states and the District of Columbia had enacted legislation regarding advance care planning. There are two broad types of advance care planning documentation: living wills and designation of a health care proxy. Although these two documents are often combined into a single document, designation of a health care proxy is not one of the primary components of a living will. The living will (or instructional directive) delineates the patient's preferences regarding treatment under different scenarios (e.g., whether condition is perceived as terminal). These documents can be very specific to a condition such as cancer, but they may also be very broad in the case of elderly individuals who are not currently suffering from a terminal condition but want to outline their wishes for care in the event of an unexpected health crisis. Examples of what this might include are general statements regarding the receipt of life-sustaining therapies and the values that should guide the decisions regarding terminal care.

I-18. **The answer is C.** *(Chap. 9)* A primary goal of palliative care medicine is to control pain in patients who are terminally ill. Surveys have found that 36–90% of individuals with advanced cancer have substantial pain, and an individualized treatment plan is necessary for each patient. For individuals with continuous pain, opioid analgesics should be administered on a scheduled basis around the clock at an interval based on the half-life of the medication chosen. Extended-release preparations are frequently used due to their longer half-lives. However, it is inappropriate to start immediately with an extended release preparation. In this scenario, the patient was treated with a continuous IV infusion via patient-controlled analgesia for 48 hours to determine her baseline opioid needs. The average daily dose of morphine required was 90 mg. This total dose should be administered in divided doses two or three times daily (either 45 mg twice daily or 30 mg three times daily). In addition, an immediate-release preparation should be available for administration for breakthrough pain. The recommended dose of the immediate release preparation is 20% of the baseline dose. In this case, the dose would be 18 mg and could be given as either 15 mg or 20 mg four times daily as needed.

I-19. **The answer is D.** *(Chap. 9)* Depression is difficult to diagnose in individuals with terminal illness and is often an overlooked symptom by physicians as many individuals believe it a normal component of terminal illness. Furthermore, symptoms commonly associated with depression such as insomnia and anorexia are also frequently seen in serious illness or occur as a side effect of treatment. Although about 75% of terminally ill patients express some depressive symptoms, only 25% or less have major depression. When assessing depression in terminally ill individuals, one should focus on symptoms pertaining to the dysphoric mood, including helplessness, hopelessness, and anhedonia. It is inappropriate to do nothing in the situation where one believes major depression is occurring. The approach to treatment should include nonpharmacologic and pharmacologic therapies. The pharmacologic approach to depression should be the same in terminally ill individuals as in non–terminally ill individuals. If an individual has a prognosis of several months or longer, selective serotonin reuptake inhibitors (fluoxetine, paroxetine) or serotonin-noradrenaline reuptake inhibitors (venlafaxine) are the preferred treatment due to their efficacy and side effect profile. However, these medications take several weeks to become effective. Thus, starting fluoxetine alone is not preferred. In patients with major depression and fatigue or opioid-induced somnolence, combining a traditional antidepressant with a psychostimulant is appropriate. Psychostimulants are also indicated in individuals with a poor prognosis who are not expected to live long enough to experience the benefits of treatment with a traditional antidepressant. A variety of psychostimulant medications are available including methylphenidate, modafinil, dextroamphetamine, or pemoline. Because this patient has a prognosis of several months or longer, methylphenidate alone is not recommended. Because of their side effect profile, tricyclic antidepressants are not used in the treatment of depression in the terminally ill unless they are utilized as adjunctive treatment for chronic pain.

I-20. **The answer is E.** *(Chap. 9)* Withdrawal of care is a common occurrence in intensive care units. More than 90% of Americans die without performance of cardiopulmonary resuscitation. When a family decides to withdraw care, the treating care team of doctors, nurses, and respiratory therapists must work together to ensure that the dying process will be comfortable for both the patient and the family. Commonly, patients receive a combination of anxiolytics and opioid analgesics. These medications also provide relief of dyspnea in the dying patient. However, they have little effect on oropharyngeal secretions. The accumulation of secretions in the oropharynx can produce agitation, labored breathing, and noisy breathing that has been labeled the "death rattle." This can be quite distressing to the family. Treatments for excessive oropharyngeal secretions are primarily anticholinergic medications including scopolamine delivered transdermally or intravenously, atropine, and glycopyrrolate. While placement of a nasal trumpet or oral airway may allow better access for suctioning of secretions, these can be uncomfortable or even painful interventions that are typically discouraged in a palliative care situation. *N*-Acetylcysteine can be used as a mucolytic agent to thin lower respiratory secretions. Pilocarpine is a cholinergic stimulant and increases salivary production.

I-21. **The answer is B.** *(Chap. 9)* It is common for patients with end-stage lung or heart disease to develop debilitating dyspnea. It is an extremely distressing symptom, possibly worse than pain for many patients. The symptom may not correlate with objective parameters like SaO_2 or $PaCO_2$. Potentially reversible or treatable causes of dyspnea include infection, pleural effusions, pulmonary emboli, pulmonary edema, asthma, and tumor encroachment on the airway. Depending on the diagnosis and the overall prognosis, specific therapy may be indicated in some cases. Opioids reduce the sensitivity of the central respiratory drive center and often reduce the sensation of dyspnea. In patients not already on an opioid, codeine is often a useful first intervention. In patients already on some opioids, morphine or another strong opioid may be used. There are no data supporting the use of nebulized morphine for dyspnea at the end of life. In the absence of bronchospasm, albuterol could worsen dyspnea as a respiratory stimulant. Benzodiazepines may help if there is concurrent anxiety but should not be used as the sole therapy for dyspnea. The use of oxygen is controversial in nonhypoxic patients. In this patient whose SaO_2 is already greater than 90% on current therapy, there is no role for increasing the FiO_2.

I-22. **The answer is A.** *(Chap. 9)* Voluntary active euthanasia is defined as intentionally administering medications or other interventions to cause the patient's death with the patient's informed consent. It is legal in Belgium and the Netherlands, but not the United States. Physician-assisted suicide (PAS) is defined as a physician providing medications or other interventions to a patient with the understanding that the patient can use them to commit suicide. This practice is legal in Montana, Oregon, Vermont, California, and Washington State. In the United States, multiple criteria must be met for PAS: the patient must have a terminal condition of <6 months, and must be determined eligible through a process that includes a 15-day waiting period. Fewer than 10–20% of terminally ill patients actually consider euthanasia and/or PAS for themselves. In the Netherlands and Oregon, >70% of patients using these interventions are dying of cancer; in Oregon, in 2013, just 1.2% of PAS cases involved patients with HIV/AIDS and 7.2% involved patients with amyotrophic lateral sclerosis. Pain is not a primary motivator for patients' requests for or interest in euthanasia and/or PAS. Fewer than 25% of all patients in Oregon cite inadequate pain control as the reason for desiring PAS. Depression, hopelessness, and, more profoundly, concerns about loss of dignity or autonomy or being a burden on family members appear to be primary factors motivating a desire for euthanasia or PAS. Over 75% cite loss of autonomy or dignity and inability to engage in enjoyable activities as the reason for wanting PAS. About 40% cite being a burden on family.

I-23. **The answer is C.** *(Chap. 10)* Sensitization occurs at the level of the peripheral nerve terminal (*peripheral sensitization*) as well as at the level of the dorsal horn of the spinal cord (*central sensitization*). Peripheral sensitization occurs in damaged or inflamed tissues, when inflammatory mediators activate intracellular signal transduction in nociceptors, prompting an increase in the production, transport, and membrane insertion of chemically gated and voltage-gated ion channels. These changes increase the excitability of nociceptor terminals and lower their threshold for activation by mechanical, thermal, and chemical stimuli. Central sensitization occurs when activity, generated by nociceptors during inflammation, enhances the excitability of nerve cells in the dorsal horn of the spinal cord. Following injury and resultant sensitization, normally innocuous stimuli can produce pain (termed *allodynia*). Sensitization is a clinically important process that contributes to tenderness, soreness, and *hyperalgesia* (increased pain intensity in response to the same noxious stimulus; e.g., pinprick causes severe pain). The convergence-projection hypothesis relates to referred pain. According to this hypothesis, visceral afferent nociceptors converge on the same pain-projection neurons as the afferents from the somatic structures in which the pain is perceived. The brain has no way of knowing the actual source of input and mistakenly "projects" the sensation to the somatic structure.

I-24. **The answer is C.** *(Chap. 10)* Lesions of the peripheral or central nociceptive pathways typically result in a loss or impairment of pain sensation. Paradoxically, damage to or dysfunction of these pathways can also produce pain. For example, damage to peripheral nerves, as occurs in diabetic neuropathy, can result in pain that is referred to the body region innervated by the damaged nerves. The tricyclic antidepressants (TCAs) that have been shown to relieve pain have significant side effects. Some of these side effects, such as orthostatic hypotension, drowsiness, cardiac conduction delay, memory impairment, constipation, and urinary retention, are particularly problematic in elderly patients, and several are additive to the side effects of opioid analgesics. The selective serotonin reuptake inhibitors such as fluoxetine (Prozac) have fewer and less serious side effects than TCAs, but they are much less effective for relieving pain. It is of interest that venlafaxine (Effexor) and duloxetine (Cymbalta), which are nontricyclic antidepressants that block both serotonin and norepinephrine reuptake, appear to retain most of the pain-relieving effect of TCAs with a side effect profile more like that of the selective serotonin reuptake inhibitors. These drugs may be particularly useful in patients who cannot tolerate the side effects of TCAs. Of the medications listed in Table I-24, duloxetine has the lowest sedative properties and amitriptyline has the highest.

TABLE I-24 Drugs for Relief of Pain

Generic Name	Dose (mg)	Interval	Comments
Nonnarcotic Analgesics: Usual Doses and Intervals			
Acetylsalicylic acid	650 PO	q4h	Enteric-coated preparations available
Acetaminophen	650 PO	q4h	Side effects uncommon
Ibuprofen	400 PO	q4–6h	Available without prescription
Naproxen	250–500 PO	q12h	Naproxen is the common NSAID that poses the least cardiovascular risk; but it has a somewhat higher incidence of gastrointestinal bleeding
Fenoprofen	200 PO	q4–6h	Contraindicated in renal disease
Indomethacin	25–50 PO	q8h	Gastrointestinal side effects common
Ketorolac	15–60 IM/IV	q4–6h	Available for parenteral use
Celecoxib	100–200 PO	q12–24h	Useful for arthritis
Valdecoxib	10–20 PO	q12–24h	Removed from U.S. market in 2005

Generic Name	Parenteral Dose (mg)	PO Dose (mg)	Comments
Narcotic Analgesics: Usual Doses and Intervals			
Codeine	30–60 q4h	30–60 q4h	Nausea common
Oxycodone	—	5–10 q4–6h	Usually available with acetaminophen or aspirin
Oxycodone extended release	—	10–40 q12h	Oral extended-release tablet; high potential for misuse
Morphine	5 q4h	30 q4h	—
Morphine sustained release	—	15–60 bid to tid	Oral slow-release preparation
Hydromorphone	1–2 q4h	2–4 q4h	Shorter acting than morphine sulfate
Levorphanol	2 q6–8h	4 q6–8h	Longer acting than morphine sulfate; absorbed well PO
Methadone	5–10 q6–8h	5–20 q6–8h	Due to long half-life, respiratory depression and sedation may persist after analgesic effect subsides; therapy should not be initiated with >40 mg/d, and dose escalation should be made no more frequently than every 3 days
Meperidine	50–100 q3–4h	300 q4h	Poorly absorbed PO; normeperidine is a toxic metabolite; routine use of this agent is not recommended
Butorphanol	—	1–2 q4h	Intranasal spray
Fentanyl	25–100 μg/h	—	72-h transdermal patch
Buprenorphine	5–20 μg/h		7-day transdermal patch
Buprenorphine	0.3 q6–8h		Parenteral administration
Tramadol	—	50–100 q4–6h	Mixed opioid/adrenergic action

	Uptake Blockade							
Generic Name	5-HT	NE	Sedative Potency	Anticholinergic Potency	Orthostatic Hypotension	Cardiac Arrhythmia	Average. Dose (mg/d)	Range (mg/d)
Antidepressants[a]								
Doxepin	++	+	High	Moderate	Moderate	Less	200	75–400
Amitriptyline	++++	++	High	Highest	Moderate	Yes	150	25–300
Imipramine	++++	++	Moderate	Moderate	High	Yes	200	75–400
Nortriptyline	+++	++	Moderate	Moderate	Low	Yes	100	40–150
Desipramine	+++	++++	Low	Low	Low	Yes	150	50–300
Venlafaxine	+++	++	Low	None	None	No	150	75–400
Duloxetine	+++	+++	Low	None	None	No	40	30–60

Generic Name	PO Dose (mg)	Interval	Generic Name	PO Dose (mg)	Interval
Anticonvulsants and Antiarrhythmics[a]					
Phenytoin	300	daily/qhs	Clonazepam	1	q6h
Carbamazepine	200–300	q6h	Gabapentin[b]	600–1200	q8h
Oxcarbazepine	300	Bid	Pregabalin	150–600	bid

[a] Antidepressants, anticonvulsants, and antiarrhythmics have not been approved by the U.S. Food and Drug Administration (FDA) for the treatment of pain.

[b] Gabapentin in doses up to 1800 mg/d is FDA approved for postherpetic neuralgia.

Abbreviations: 5-HT, serotonin; NE, norepinephrine; NSAID, nonsteroidal anti-inflammatory drug.

I-25. **The answer is C.** *(Chap. 10)* Substance P is released from primary afferent nociceptors and has multiple biological activities. It is a potent vasodilator, degranulates mast cells, is a chemoattractant for leukocytes, and increases the production and release of inflammatory mediators. Interestingly, depletion of substance P from joints reduces the severity of experimental arthritis. Phosphodiesterase inhibitors increase intracellular concentration of cyclic guanosine monophosphate or cyclic adenosine monophosphate.

I-26. **The answer is C.** *(Chap. 10)* This patient has complex regional pain syndrome. Patients with peripheral nerve injury occasionally develop spontaneous pain in the region innervated by the nerve. This pain is often described as having a burning quality. The pain typically begins after a delay of hours to days or even weeks and is accompanied by swelling of the extremity, periarticular bone loss, and arthritic changes in the distal joints. The pain may be relieved by a local anesthetic block of the sympathetic innervation to the affected extremity. Damaged primary afferent nociceptors acquire adrenergic sensitivity and can be activated by stimulation of the sympathetic outflow. This constellation of spontaneous pain and signs of sympathetic dysfunction following injury has been termed complex regional pain syndrome (CRPS). When this occurs after an identifiable nerve injury, it is termed CRPS type 2 (also known as posttraumatic neuralgia or, if severe, causalgia). When a similar clinical picture appears without obvious nerve injury, it is termed CRPS type 1 (also known as reflex sympathetic dystrophy). CRPS can be produced by a variety of injuries, including fractures of bone, soft tissue trauma, myocardial infarction, and stroke. CRPS type 1 typically resolves with symptomatic treatment; however, when it persists, detailed examination often reveals evidence of peripheral nerve injury. Although the pathophysiology of CRPS is poorly understood, the pain and the signs of inflammation, when acute, can be rapidly relieved by blocking the sympathetic nervous system. This implies that sympathetic activity can activate undamaged nociceptors when inflammation is present. Signs of sympathetic hyperactivity should be sought in patients with posttraumatic pain and inflammation and no other obvious explanation. Acute gonococcal arthritis and gout will have a focal joint fluid collection and inflammation. Systemic lupus can manifest in cryptic joint findings, but in this case, the focality and absence of systemic findings or serologic abnormalities make it less likely. Carpal tunnel syndrome, caused by injury to the median nerve, is not consistent with this presentation of the entire arm.

I-27. **The answer is D.** *(Chap. 10)* Nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin inhibit cyclooxygenase (COX) and have anti-inflammatory actions. They are particularly effective for mild to moderate headache and for pain of musculoskeletal origin. Because they are effective for these common types of pain and are available without a prescription, COX inhibitors are by far the most commonly used analgesics. With chronic use, gastric irritation is a common side effect of aspirin and NSAIDs and is the problem that most frequently limits the dose that can be given. Gastric irritation is most severe with aspirin, which may cause erosion and ulceration of the gastric mucosa, leading to bleeding or perforation. Because aspirin irreversibly acetylates platelet cyclooxygenase and thereby interferes with coagulation of the blood, gastrointestinal bleeding is a particular risk. Older age and history of gastrointestinal disease increase the risks of aspirin and NSAIDs. In addition to the well-known gastrointestinal toxicity of NSAIDs, nephrotoxicity is a significant problem for patients using these drugs on a chronic basis. Patients at risk for renal insufficiency, particularly those with significant contraction of their intravascular volume as occurs with chronic diuretic use or acute hypovolemia, should be monitored closely. NSAIDs can also increase blood pressure in some individuals. Long-term treatment with NSAIDs requires regular blood pressure monitoring and treatment if necessary. There are two major classes of COX: COX-1 is constitutively expressed, and COX-2 is induced in the inflammatory state. COX-2-selective drugs have similar analgesic potency and produce less gastric irritation than the nonselective COX inhibitors. The use of COX-2-selective drugs does not appear to lower the risk of nephrotoxicity compared with nonselective NSAIDs. On the other hand, COX-2-selective drugs offer a significant benefit in the management of acute postoperative pain because they do not affect blood coagulation. Nonselective COX inhibitors are usually contraindicated postoperatively because they impair platelet-mediated blood clotting and are thus associated with increased bleeding at the operative site. COX-2 inhibitors, including celecoxib (Celebrex), are associated with increased cardiovascular risk. It appears that this is a class effect of NSAIDs, excluding aspirin. These drugs are contraindicated in patients in the immediate period after coronary artery bypass surgery and should be used with caution in elderly patients and those with a history of or significant risk factors for cardiovascular disease.

I-28. **The answer is E.** *(Chap. 10)* Opioids, such as oxycodone, work centrally and may cause significant respiratory depression and sedation. Because of hypoventilation, hypoxemia is common although easily treated with supplemental oxygen. Naloxone is an opioid antagonist that may rapidly reverse the respiratory depression and sedation. Alvimopan is an oral opioid antagonist that is confined to the gut. It may be useful to counteract peripheral opioid side effects, such as constipation, but has no central actions. Albuterol is a β-agonist that may increase respiratory rate but will not reverse the opioid sedation. Flumazenil is a γ-aminobutyric acid (GABA) receptor antagonist that can be used for benzodiazepine overdose. *N*-Acetylcysteine is used for acetaminophen overdose. Many forms of oxycodone also include acetaminophen, so the clinician should be careful to elicit an accurate medication history because of the possibility of concurrent acetaminophen-induced liver toxicity.

I-29. **The answer is A.** *(Chap. 11)* Myocardial ischemia causing chest discomfort, termed *angina pectoris*, is a primary clinical concern in patients presenting with chest symptoms. The site of the discomfort is usually retrosternal, not inframammary, but radiation is common and generally occurs down the ulnar surface of the left arm; the right arm, both arms, neck, jaw, or shoulders may also be involved (Figure I-29). The neural pathways involved in ischemic cardiac pain are poorly understood but can cause a pressure-like sensation. Ischemic episodes are thought to excite local chemosensitive and mechanoreceptive receptors that, in turn, stimulate the release of adenosine, bradykinin, and other substances that activate the sensory ends of sympathetic and vagal afferent fibers. The afferent fibers traverse the nerves that connect to the upper five thoracic sympathetic ganglia and upper five distal thoracic roots of the spinal cord. From there, impulses are transmitted to the thalamus. Within the spinal cord, cardiac

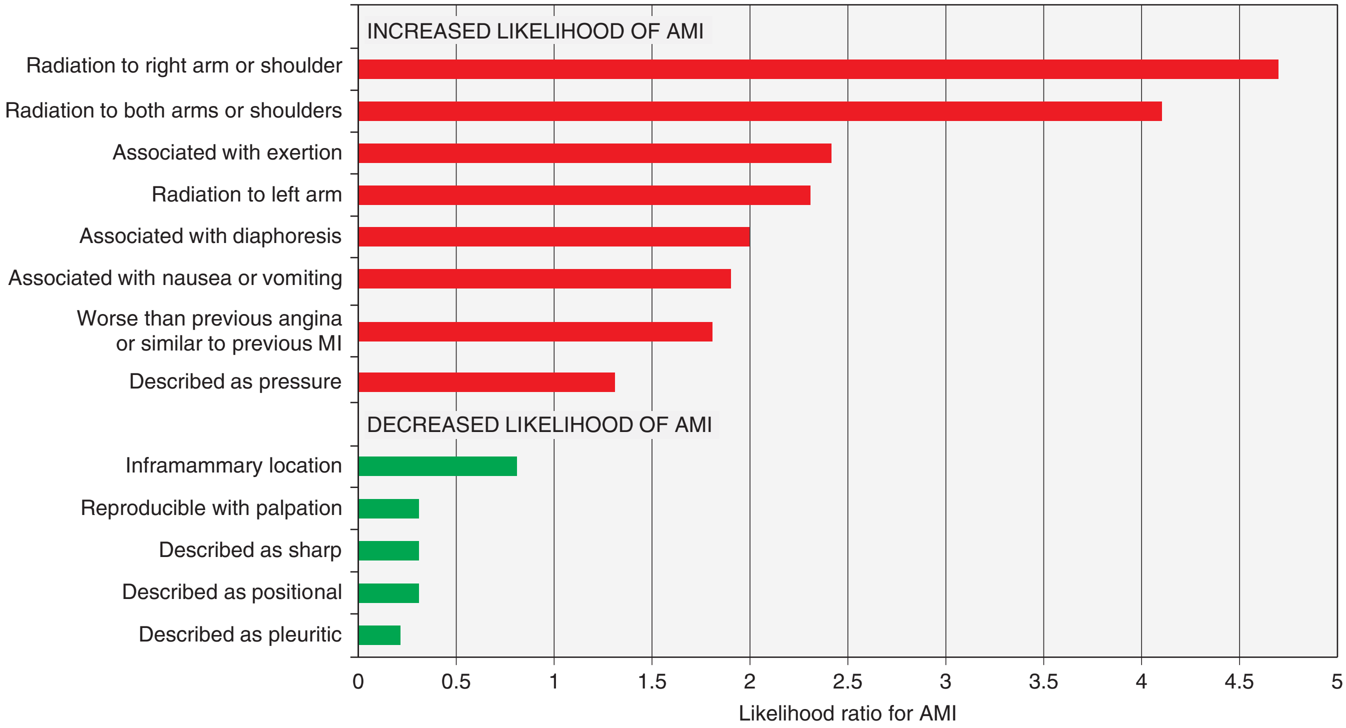


FIGURE I-29 Data from Swap CJ, Nagurney JT: Value and limitations of chest pain history in the evaluation of patients with suspected acute coronary syndromes. *JAMA* 294:2623, 2005.

sympathetic afferent impulses may converge with impulses from somatic thoracic structures, and this convergence may be the basis for referred cardiac pain. In addition, cardiac vagal afferent fibers synapse in the nucleus tractus solitarius of the medulla and then descend to the upper cervical spinothalamic tract, and this route may contribute to anginal pain experienced in the neck and jaw.

I-30. **The answer is B.** *(Chap. 11)* Chest discomfort is the third most common reason for visits to the emergency department (ED) in the United States, resulting in 6–7 million emergency visits each year (Figure I-30). More than 60% of patients with this presentation are hospitalized for further testing, and the rest undergo additional investigation in the ED. Fewer than 25% of evaluated patients are eventually diagnosed with acute coronary syndrome (ACS), with rates of 5–15% in most series of unselected populations. In the remainder, the most common diagnoses are gastrointestinal causes, and fewer than 10% are other life-threatening cardiopulmonary conditions. In a large proportion of patients with transient acute chest discomfort, ACS or another acute cardiopulmonary cause is excluded, but the cause is not determined. A disconcerting 2–6% of patients with chest discomfort of presumed nonischemic etiology who are discharged from the ED are later deemed to have had a missed myocardial infarction (MI). Patients with a missed diagnosis of MI have a 30-day risk of death that is double that of their counterparts who are hospitalized.

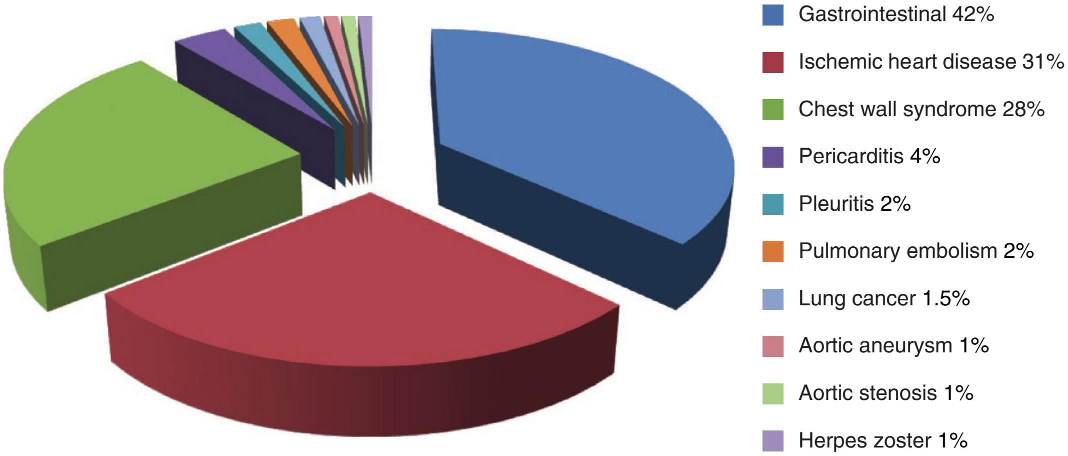


FIGURE I-30 Data from Fruergaard P et al: The diagnoses of patients admitted with acute chest pain but without myocardial infarction. *Eur Heart J* 17:1028, 1996.

I-31. **The answer is B.** *(Chap. 13)* Acute, maximal in <5 minutes, and severe headache lasting >5 minutes with stiff neck but without fever suggests subarachnoid hemorrhage. A ruptured aneurysm, arteriovenous malformation, or intraparenchymal hemorrhage may also present with headache alone. Rarely, if the hemorrhage is small or below the foramen magnum, the noncontrast head CT scan can be normal. Therefore, lumbar puncture may be required to diagnose definitively subarachnoid hemorrhage. The other options are appropriate tests for other causes of headache. Ophthalmic examination is appropriate if glaucoma is suspected. Laboratory testing and temporal artery biopsy would be appropriate if temporal arteritis is suspected. These are less likely given the age of the patient and the acute history.

I-32. **The answer is E.** *(Chap. 13)* The patient who presents with a new, severe headache has a differential diagnosis that is quite different from the patient with recurrent headaches over many years. In new-onset and severe headache, the probability of finding a potentially serious cause is considerably greater than in recurrent headache (Table I-32). Patients with recent onset of pain require prompt evaluation and appropriate treatment. Serious causes to be considered include meningitis, subarachnoid hemorrhage, epidural or subdural hematoma, glaucoma, tumor, and purulent sinusitis. When worrisome symptoms

TABLE I-32 Headache Symptoms That Suggest a Serious Underlying Disorder

Sudden-onset headache
First severe headache
“Worst” headache ever
Vomiting that precedes headache
Subacute worsening over days or weeks
Pain induced by bending, lifting, cough
Pain that disturbs sleep or presents immediately upon awakening
Known systemic illness
Onset after age 55
Fever or unexplained systemic signs
Abnormal neurologic examination
Pain associated with local tenderness, e.g., region of temporal artery

and signs are present, rapid diagnosis and management are critical. A careful neurologic examination is an essential first step in the evaluation. In most cases, patients with an abnormal examination or a history of recent-onset headache should be evaluated by a CT or MRI study. As an initial screening procedure for intracranial pathology in this setting, CT and MRI methods appear to be equally sensitive. Brain tumor is a rare cause of headache and even less commonly a cause of severe pain. The vast majority of patients presenting with severe headache have a benign cause.

I-33. **The answer is D.** *(Chap. 14)* The evidence regarding treatment for neck pain is less comprehensive than that for low back pain, but the approach is remarkably similar in many respects. As with low back pain, spontaneous improvement is the norm for acute neck pain. The usual goals of therapy are to promote a rapid return to normal function and provide pain relief while healing proceeds. In addition to medications for the relief of chronic neck and back pain, other types of therapies have been used to successfully treat pain. For patients with chronic neck pain, supervised exercise programs can provide symptom relief and improve function. Massage can produce temporary pain relief. Acupuncture provided short-term benefit for some patients compared with a sham procedure and is an option. Spinal manipulation alone has not been shown to be effective and carries a risk for injury. Surgical treatment for chronic neck pain without radiculopathy or spine instability is not recommended.

I-34. **The answer is E.** *(Chap. 14)* Radicular pain is typically sharp and radiates from the low back to a leg within the territory of a nerve root. Coughing, sneezing, or voluntary contraction of abdominal muscles (lifting heavy objects or straining at stool) may elicit the radiating pain. The pain may increase in postures that stretch the nerves and nerve roots. Sitting with the leg outstretched places traction on the sciatic nerve and L5 and S1 roots because the nerve passes posterior to the hip. The femoral nerve (L2, L3, and L4 roots) passes anterior to the hip and is not stretched by sitting. The straight-leg raising (SLR) maneuver is a simple bedside test for nerve root disease. With the patient supine, passive flexion of the extended leg at the hip stretches the L5 and S1 nerve roots and the sciatic nerve. Passive dorsiflexion of the foot during the maneuver adds to the stretch. In healthy individuals, flexion to at least 80 degrees is normally possible without causing pain, although a tight, stretching sensation in the hamstring muscles is common. The SLR test is positive if the maneuver reproduces the patient’s usual back or limb pain. The patient may describe pain in the low back, buttocks, posterior thigh, or lower leg, but the key feature is reproduction of the patient’s usual pain. The crossed SLR sign is present when flexion of one leg reproduces the usual pain in the opposite leg or buttocks. In disk herniation, the crossed SLR sign is less sensitive but more specific than the SLR sign. The reverse SLR sign is elicited by standing the patient next to the examination table and passively extending each leg with the knee fully extended. This maneuver, which stretches the L2–L4 nerve roots, lumbosacral plexus, and femoral nerve, is considered positive if the patient’s usual back or limb pain is reproduced. For all of these tests, the nerve or nerve root lesion is always on the side of the pain (Table I-34).

TABLE I-34 Lumbosacral Radiculopathy: Neurologic Features

Lumbosacral Nerve Roots	Examination Findings			Pain Distribution
	Reflex	Sensory	Motor	
L2	—	Upper anterior thigh	Psoas (hip flexors)	Anterior thigh
L3	—	Lower anterior thigh	Psoas (hip flexors)	Anterior thigh, knee
—	—	Anterior knee	Quadriceps (knee extensors)	—
—	—	—	Thigh adductors	—
L4	Quadriceps (knee)	Medial calf	Quadriceps (knee extensors)[a]	Knee, medial calf
—	—	—	Thigh adductors	Anterolateral thigh
L5	—	Dorsal surface—foot	Peronei (foot evertors)[a]	Lateral calf, dorsal foot, posterolateral thigh, buttocks
—	—	Lateral calf	Tibialis anterior (foot dorsiflexors)	—
—	—	—	Gluteus medius (leg abductors)	—
—	—	—	Toe dorsiflexors	—
S1	Gastrocnemius/soleus (ankle)	Plantar surface—foot	Gastrocnemius/soleus (foot plantar flexors)[a]	Bottom foot, posterior calf, posterior thigh, buttocks
—	—	Lateral aspect—foot	Abductor hallucis (toe flexors)[a]	—
—	—	—	Gluteus maximus (leg extensors)	—

[a] These muscles receive the majority of innervation from this root.

I-35. **The answer is B.** *(Chap. 14)* The prognosis for acute low back and leg pain with radiculopathy due to disk herniation is generally favorable, with most patients showing substantial improvement over months. Serial imaging studies suggest spontaneous regression of the herniated portion of the disk in two-thirds of patients over 6 months. Nonetheless, there are several important treatment options to provide symptomatic relief while this natural healing process unfolds. Resumption of normal activity is recommended. Randomized trial evidence suggests that bedrest is ineffective for treating sciatica as well as back pain alone. Acetaminophen and nonsteroidal anti-inflammatory drugs are useful for pain relief, although severe pain may require short courses of opioid analgesics. Epidural glucocorticoid injections have a role in providing temporary symptom relief for sciatica due to a herniated disk. However, there does not appear to be a benefit in terms of reducing subsequent surgical interventions. Surgical intervention is indicated for patients who have progressive motor weakness due to nerve root injury demonstrated on clinical examination or electromyography.

I-36 and I-37. **The answers are C and B, respectively.** *(Chap. 14)* This patient has lumbar spinal stenosis (LSS). LSS is due to a narrowed lumbar spinal canal and, although it may cause symptoms as described in the question, it is also frequently asymptomatic. Typical is neurogenic claudication, consisting of back and buttock or leg pain induced by walking or standing and relieved by sitting. Symptoms in the legs are usually bilateral. Unlike vascular claudication, symptoms are often provoked by standing without walking. Unlike lumbar disk disease, symptoms are usually relieved by sitting. Patients with neurogenic claudication can often walk much farther when leaning over a shopping cart and can pedal a stationary bike with ease while sitting. These flexed positions increase the anteroposterior spinal canal diameter and reduce intraspinal venous hypertension, resulting in pain relief. Focal weakness, sensory loss, or reflex changes may occur when spinal stenosis is associated with neural foraminal narrowing and radiculopathy. Severe neurologic deficits, including paralysis and urinary incontinence, occur only rarely. LSS by itself is frequently asymptomatic, and the correlation between the severity of symptoms and degree of stenosis of the spinal canal is variable. Conservative treatment of symptomatic LSS includes nonsteroidal anti-inflammatory drugs, acetaminophen, exercise programs, and symptomatic treatment of acute pain episodes. Surgical therapy is considered when medical therapy does not relieve symptoms sufficiently to allow for resumption of activities of daily living or when focal neurologic signs are present. Most patients with neurogenic claudication who are treated medically do not improve over time. Surgical management can produce significant relief of back and leg pain within 6 weeks, and pain relief persists for at least 2 years. However, up to one-quarter of patients develop recurrent stenosis at the same spinal level or an adjacent level 7–10 years after the initial surgery; recurrent symptoms usually respond to a second surgical decompression. There is insufficient evidence to support the routine use of epidural glucocorticoid injections.

I-38 and I-39. **The answers are B and C, respectively.** *(Chap. 14)* Surveys in the United States indicate that patients with back pain have reported progressively worse functional limitations in recent years, despite rapid increases in spine imaging, opioid prescribing, injections, and spine surgery. This suggests that more selective use of diagnostic and treatment modalities may be appropriate. Spine imaging often reveals abnormalities of dubious clinical relevance that may alarm clinicians and patients and prompt further testing and unnecessary therapy. Both randomized trials and observational studies have suggested a "cascade effect" of imaging, which may create a gateway to other unnecessary care. Based in part on such evidence, the American College of Physicians has made parsimonious spine imaging a high priority in its "Choosing Wisely" campaign, aimed at reducing unnecessary care. Successful efforts to reduce unnecessary imaging have included physician education by clinical leaders, computerized decision support to identify recent imaging tests and eliminate duplication, and requiring an approved indication to order an imaging test. Acute lumbar back pain (ALBP) is defined as pain of <3 months in duration without leg pain. Most patients have purely "mechanical" symptoms (i.e., pain that is aggravated by motion and relieved by rest). The initial assessment excludes serious causes of spine pathology that require urgent intervention including infection, cancer, or trauma (see Table I-39). Laboratory and imaging studies are unnecessary if risk factors are absent. CT, MRI, and plain spine films are rarely indicated in the first month of symptoms unless a spine fracture, tumor, or infection is suspected. The prognosis is generally excellent. Many patients do not seek medical care and improve on their own with resumption of normal activities. Even among those seen in primary care, two-thirds report being substantially improved after 7 weeks. This spontaneous improvement can mislead clinicians and researchers about the efficacy of treatment interventions unless subjected to rigorous prospective trials. Many treatments commonly used in the past but now known to be ineffective, including bedrest and lumbar traction, have been largely abandoned. Clinicians should reassure patients that improvement is very likely and instruct them in self-care. Education is an important part of treatment. Evidence-based guidelines recommend over-the-counter medicines such as acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) as first-line options for treatment of ALBP. Skeletal muscle relaxants, such as cyclobenzaprine or methocarbamol, may be useful, but sedation is a common side effect.

TABLE I-39 **Acute Low Back Pain: Risk Factors for an Important Structural Cause**

History
Pain worse at rest or at night
Prior history of cancer
History of chronic infection (especially lung, urinary tract, skin)
History of trauma
Incontinence
Age >70 years
IV drug use
Glucocorticoid use
History of a rapidly progressive neurologic deficit
Examination
Unexplained fever
Unexplained weight loss
Palpation/percussion tenderness over the midline spine
Abdominal, rectal, or pelvic mass
Internal/external rotation of the leg at the hip; heel percussion sign
Straight leg- or reverse straight leg-raising signs
Progressive focal neurologic deficit

Limiting the use of muscle relaxants to nighttime only may be an option for patients with back pain that interferes with sleep. There is no good evidence to support the use of opioid analgesics or tramadol as first-line therapy for ALBP. Their use is best reserved for patients who cannot tolerate acetaminophen or NSAIDs or for those with severe refractory pain. There is no evidence to support the use of oral or injected glucocorticoids for ALBP without radiculopathy. Similarly, therapies for neuropathic pain, such as gabapentin or tricyclic antidepressants, are not indicated for ALBP. Nonpharmacologic treatments for ALBP include spinal manipulation, exercise, physical therapy, massage, acupuncture, transcutaneous electrical nerve stimulation, and ultrasound. Spinal manipulation appears to be roughly equivalent to conventional medical treatments and may be a useful alternative for patients who wish to avoid or who cannot tolerate drug therapy. There is little evidence to support the use of physical therapy, massage, acupuncture, laser therapy, therapeutic ultrasound, corsets, or lumbar traction. Although important for chronic pain, back exercises for ALBP are generally not supported by clinical evidence. There is no convincing evidence regarding the value of ice or heat applications for ALBP; however, many patients report temporary symptomatic relief from ice or frozen gel packs, and heat may produce a short-term reduction in pain after the first week.

I-40. **The answer is A.** *(Chap. 15) Fever* is an elevation of body temperature that exceeds the normal daily variation and occurs *in conjunction with an increase in the hypothalamic set point* (e.g., from 37°C to 39°C [98.6°F to 102°F]). It is important to distinguish between fever and hyperthermia because hyperthermia can be rapidly fatal and characteristically does not respond to antipyretics. Hyperthermia is characterized by an uncontrolled increase in body temperature that exceeds the body's ability to lose heat. The setting of the hypothalamic thermoregulatory center is unchanged. Hyperthermia is often diagnosed on the basis of the events immediately preceding the elevation of core temperature; e.g., heat exposure or treatment with drugs that interfere with thermoregulation. In patients with heat stroke syndromes and in those taking drugs that block sweating, the skin is hot but dry, whereas in fever the skin can be cold as a consequence of vasoconstriction. In contrast to fever in infections, hyperthermia does not involve pyrogenic molecules. Antipyretics do not reduce the elevated temperature in hyperthermia, whereas in fever and even in hyperpyrexia, adequate doses of either aspirin or acetaminophen usually result in some decrease in body temperature.

I-41. **The answer is B.** *(Chap. 15)* Children with a history of febrile or nonfebrile seizure should be aggressively treated to reduce fever. However, it is unclear what triggers the febrile seizure, and there is no correlation between absolute temperature elevation and onset of a febrile seizure in susceptible children. In children, acetaminophen or oral ibuprofen must be used because aspirin increases the risk of Reye syndrome. If the patient cannot take oral antipyretics, parenteral preparations of nonsteroidal anti-inflammatory drugs and rectal suppositories of various antipyretics can be used.

I-42. **The answer is A.** *(Chap. 16) Rubella* (German measles) also spreads from the hairline downward; unlike that of measles; however, the rash of rubella tends to clear from originally affected areas as it migrates, and it may be pruritic. Forchheimer spots (palatal petechiae) may develop but are nonspecific. The rash of *rubeola* (measles) starts at the hairline 2–3 days into the illness and moves down the body, typically sparing the palms and soles. It begins as discrete erythematous lesions, which become confluent as the rash spreads. Koplik spots (1- to 2-mm white or bluish lesions with an erythematous halo on the buccal mucosa) are pathognomonic for measles and are generally seen during the first 2 days of symptoms. They should not be confused with Fordyce spots (ectopic sebaceous glands), which have no erythematous halos and are found in the mouth of healthy individuals. Koplik spots may briefly overlap with the measles exanthem. Although drug reactions have many manifestations, maculopapular drug-induced eruptions are most common. Eruptions from drugs tend to be more intensely pruritic, although this is not reliable to distinguish them, it would not be expected to cause arthritis and posterior auricular lymphadenopathy. Lyme disease is the most common tick-borne infection in New York but erythema migrans, the rash of *Lyme disease,* typically manifests as single or multiple annular lesions. Untreated erythema migrans lesions usually fade within a month but may persist for more than a year. Acute HIV can present with lymphadenopathy and arthritis; however, it typically presents with a macular, roseola-like rash with acute seroconversion.

I-43. **The answer is C.** *(Chap. 16)* The patient's presentation is consistent with acute HIV infection. It is estimated that 50–70% of individuals with HIV infection experience an acute clinical syndrome 3–6 weeks after primary infection. Acute bronchitis and sinusitis are prevalent during all stages of HIV infection, and thrush is a common initial presentation (as seen in Figure I-43). Thrush appears as a white, cheesy exudate, often on an erythematous mucosa in the posterior oropharynx. Although most commonly seen on the soft palate, early lesions are often found along the gingival border. The diagnosis is made by direct examination of a scraping for pseudohyphal elements. The rash is not consistent with herpes zoster, which typically presents in a dermatomal distribution. His examination does not support epiglottitis as he has no drooling or dysphagia. A rare but feared complication of measles is subacute sclerosing panencephalitis; however, this patient does not have the typical rash of measles and has been vaccinated against it. Splenic rupture occasionally occurs with infectious mononucleosis, but this patient has no lymphadenopathy or splenomegaly to suggest this diagnosis and the oral findings are consistent with thrush.

I-44. **The answer is D.** *(Chaps. 16 and 182)* All of the causative agents listed are associated with rashes that can extend to the palms and soles. *Chikungunya fever*, which is transmitted by mosquito bite in tropical and subtropical regions, is associated with a maculopapular eruption and severe polyarticular small-joint arthralgias. *Hand-foot-and-mouth disease*, most commonly caused by coxsackievirus A16 or enterovirus 71, is distinguished by tender vesicles distributed on the hands and feet and in the mouth; coxsackievirus A6 causes an atypical syndrome with more extensive lesions. The rash of *secondary syphilis* (caused by *Treponema pallidum*), which may be generalized, is prominent on the palms and soles. *Rickettsia rickettsii* is the cause of Rocky Mountain spotted fever, which is spread by ticks and is widespread through the United States with most cases in the southeast and central southwest. It typically manifests as a rash beginning on the wrists and ankles and spreads centripetally. The rash appears on palms and soles later in the disease, and lesions display evolution from blanchable macules to petechiae.

I-45. **The answer is A.** *(Chap. 16)* Individuals with classic urticaria ("hives") usually have a hypersensitivity reaction without associated fever. In the presence of fever, urticaria-like eruptions are most often due to *urticarial vasculitis*. Unlike individual lesions of classic urticaria, which lasts up to 24 hours, these lesions may last 3–5 days. Etiologies include serum sickness (often induced by drugs such as penicillins, sulfas, salicylates, or barbiturates), connective-tissue disease (e.g., systemic lupus erythematosus or Sjögren syndrome), and infection (e.g., with hepatitis B virus, enteroviruses, or parasites). Malignancy, especially lymphoma, may be associated with fever and chronic urticaria.

I-46. **The answer is C.** *(Chap. 16)* This patient likely has toxic shock syndrome, given the clinical appearance of septic shock with no positive blood cultures. The characteristic diffuse rash, as well as the lack of a primary infected site, make *Staphylococcus* the more likely inciting agent. Streptococcal toxic shock usually has a prominent primary site of infection, but the diffuse rash is usually much more subtle than in this case. Staphylococcal toxic shock can be associated with immunosuppression, surgical wounds, or retained tampons. Mere *Staphylococcus aureus* colonization (with an appropriate toxigenic strain) can incite toxic shock; overt infection is not necessary. Centers for Disease Control and Prevention guidelines state that measles, Rocky Mountain spotted fever, and leptospirosis need to be ruled out serologically to confirm the diagnosis. However, this patient is at very low risk for these diagnoses based on vaccination and travel history. Juvenile rheumatoid arthritis would be a consideration only if the fevers were more prolonged and there was documented evidence of organomegaly and enlarged lymph nodes.

I-47. The answer is C. *(Chaps. 16 and 181)* This is a classic picture of erythema migrans due to *Borrelia burgdorferi*, or Lyme disease. The rash is an early manifestation of Lyme disease and is characterized by erythematous annular patches, often with a central erythematous focus at the tick bite site. The sequelae of Lyme disease are myriad and include central nervous system, articular, and cardiac complications. One of the classic cardiac complications is conduction system disease, most likely concerning the possibility of progression to complete heart block. Option B describes the classic cutaneous manifestations of Kawasaki disease, most commonly seen in children. When seen in conjunction with painful or nonpainful purpuric lesions on the hands or feet, the murmur of mitral regurgitation would suggest infectious endocarditis (option A). Option D describes a toxic shock syndrome, which is unlikely in this patient with erythema migrans. Option E describes Koplik spots, which are the pathognomonic buccal mucosal findings in measles.

I-48. The answer is A. *(Chaps. 16 and 56)* This patient exhibits classic findings of the drug reaction with eosinophilia and systemic symptoms syndrome (DRESS). Some individuals are genetically unable to detoxify arene oxides present in some anticonvulsants (e.g., phenobarbital) and are susceptible to this dire syndrome. The confluence of the desquamative rash, eosinophilia, hepatic involvement, facial edema, and hypotension are all typical of this disease. Sweet syndrome, or acute febrile neutrophilic dermatosis, is characterized by erythematous indurated plaque with a pseudovesicular border. In 20% of cases, Sweet syndrome is associated with malignancy (usually hematologic), but it can also be associated with infections, inflammatory bowel disease, or pregnancy. Erythema multiforme is characterized by target lesions (central erythema surrounded by area of clearing and another rim of erythema) up to 2 cm, which are symmetric on the knees, elbows, palms, and soles and spread centripetally. It is often confused with Stevens-Johnson syndrome, although erythema multiforme lacks the marked skin sloughing seen in Stevens-Johnson syndrome. Staphylococcal toxic shock syndrome is a consideration here, as the hypotension and skin rash are typical. However, the lack of a cutaneous lesion or other risk factors and the concomitant eosinophilia and hepatitis make DRESS the more likely diagnosis.

I-49. The answer is C. *(Chap. 16)* This is erythema nodosum, a panniculitis classically found on the lower extremities characterized by exquisitely tender nodules and plaques. It has several associated disease etiologies including infections (streptococcal, fungal, mycobacterial, yersinial), drugs (sulfas, penicillins, oral contraceptives), sarcoidosis, and other autoimmune diseases such as inflammatory bowel disease. Lung cancer is not a classically associated disease for erythema nodosum.

I-50. The answer is E. *(Chap. 17)* Fever of unknown origin is now defined as follows:

1. Fever ≥38.3°C (≥101°F) on at least two occasions.
2. Illness duration of ≥3 weeks.
3. No known immunocompromised state.
4. Diagnosis that remains uncertain after a thorough history taking, physical examination, and the following obligatory investigations: determination of erythrocyte sedimentation rate and C-reactive protein level; platelet count; leukocyte count and differential; measurement of levels of hemoglobin, electrolytes, creatinine, total protein, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, creatine kinase, ferritin, antinuclear antibodies (ANAs), and rheumatoid factor; protein electrophoresis; urinalysis; blood cultures ($n = 3$); urine culture; chest x-ray; abdominal ultrasonography; and tuberculin skin test or interferon-γ release assay.

The patient listed in option A only had fevers for a short period of time. The patient described in option B meets criteria for lupus with lupus malar rash, oral ulcers, joint disease, and ANA greater than the laboratory reference range. The patient described in option C only has subjective fevers without any documented fevers. Patient D is immunocompromised due to prolonged steroid exposure.

I-51. **The answer is C.** *(Chap. 17)* In general, infection accounts for about one-fifth of the cases of fever of unknown origin (FUO) in Western countries; next in frequency are noninfectious inflammatory diseases (NIIDs; which include "collagen or rheumatic diseases," vasculitis syndromes, granulomatous disorders, and autoinflammatory syndromes) and neoplasms. In geographic areas outside the West, infections are a much more common cause of FUO (43% vs 17%), whereas the proportions of cases due to NIIDs and neoplasms are similar. It is important to remember that FUO is far more often caused by an atypical presentation of a rather common disease than by a very rare disease. Atypical presentations of endocarditis, diverticulitis, vertebral osteomyelitis, and extrapulmonary tuberculosis are the more common infectious disease diagnoses. Of the NIIDs, large-vessel vasculitis, polymyalgia rheumatica, sarcoidosis, familial Mediterranean fever, and adult-onset Still disease are rather common diagnoses in patients with FUO. Previous studies of FUO have shown that a diagnosis is more likely in elderly patients than in younger age groups. In the West, the proportion of patients who remain undiagnosed is higher than in non-Western populations and has been increasing over figures reported in studies before the 1990s. An important factor contributing to the seemingly high diagnostic failure rate is that a diagnosis is more often established before 3 weeks have elapsed, given that patients with fever tend to seek medical advice earlier and that better diagnostic techniques, such as CT and MRI, are available; therefore, only the cases that are most difficult to diagnose continue to meet the criteria for FUO. Malignancy accounts for most FUO-related deaths. FUO-related mortality rates have continuously declined over recent decades. The majority of fevers are caused by treatable diseases, and the risk of death related to FUO is, of course, dependent on the underlying disease.

I-52. **The answer is C.** *(Chap. 17)* Fever of unknown origin (FUO) is defined as the presence of fevers >38.3°C (101°F) on several occasions occurring for >3 weeks without a defined cause after appropriate investigation into potential causes have failed to yield a diagnosis. Initial laboratory investigation into an FUO should include a complete blood count with differential, peripheral blood smear, erythrocyte sedimentation rate, C-reactive protein, electrolytes, creatinine, calcium, liver function tests, urinalysis, and muscle enzymes. In addition, specific testing for a variety of infections should be performed, including Venereal Disease Research Laboratory test for syphilis; HIV, cytomegalovirus, Epstein-Barr virus, and positive protein derivative testing; and blood, sputum, and urine cultures, if appropriate. Finally, the workup should include evaluation for inflammatory disorders. These tests include antinuclear antibodies, rheumatoid factor, ferritin, iron, and transferrin. This patient has had a significant workup that has demonstrated primarily nonspecific findings, including elevation in the erythrocyte sedimentation rate and ferritin as well as borderline enlargement of multiple lymph nodes. The only finding so far that may help define further workup is the elevation in calcium levels. When combined with the clinical symptoms and prominent lymph nodes, this could suggest granulomatous diseases, including disseminated tuberculosis, fungal infections, or sarcoidosis. The next step in the workup of this patient would be to obtain a sample from an enlarged lymph node for cultures and pathology to confirm granulomatous inflammation and provide additional samples for microbiology. In recent studies, up to 30% of individuals will not have an identified cause of FUO, and infectious etiologies continue to comprise approximately 25% of all FUO in the United States. The most common infection causing FUO is extrapulmonary tuberculosis. However, one would not consider empirical therapy if the possibility to obtain definitive diagnosis exists through a procedure such as a needle biopsy, because it is prudent to have not only the diagnosis but also the sensitivity profile of the organism to ensure appropriate therapy. Even in the presence of granulomatous infection, sarcoidosis would be considered a diagnosis of exclusion and would require definitive negative mycobacterial cultures prior to considering therapy with corticosteroids. Serum angiotensin-converting enzyme levels are neither appropriately sensitive nor specific for diagnosis of sarcoidosis and should not be used to determine whether therapy is needed. Positron emission tomography-computed tomography (PET-CT) imaging would be unlikely to be helpful to diagnose malignancy in this situation as the presence of granulomatous inflammation can lead to false-positive results or will confirm the presence of already characterized abnormal lymph nodes.

I-53. The answer is A. *(Chap. 18)* Syncope is a common presenting problem, accounting for ~3% of all emergency room visits and 1% of all hospital admissions. The annual cost for syncope-related hospitalization in the United States is ~$2.4 billion. Syncope has a lifetime cumulative incidence of up to 35% in the general population. Neurally mediated syncope is the etiology in the vast majority of these cases. In elderly adults, there is a sharp rise in the incidence of syncope after 70 years. Orthostatic hypotension also increases in prevalence with age because of the reduced baroreflex responsiveness, decreased cardiac compliance, and attenuation of the vestibulosympathetic reflex associated with aging. In the elderly, orthostatic hypotension is substantially more common in institutionalized (54–68%) than community-dwelling (6%) individuals, an observation most likely explained by the greater prevalence of predisposing neurologic disorders, physiologic impairment, and vasoactive medication use among institutionalized patients. The mortality rate is increased in individuals with syncope due to orthostatic hypotension related to age and the associated comorbid conditions (Table I-53).

TABLE I-53 High-Risk Features Indicating Hospitalization or Intensive Evaluation of Syncope

Chest pain suggesting coronary ischemia
Features of congestive heart failure
Moderate or severe valvular disease
Moderate or severe structural cardiac disease
Electrocardiographic features of ischemia
History of ventricular arrhythmias
Prolonged QT interval (>500 ms)
Repetitive sinoatrial block or sinus pauses
Persistent sinus bradycardia
Bi- or trifascicular block or intraventricular conduction delay with QRS duration ≥120 ms
Atrial fibrillation
Nonsustained ventricular tachycardia
Family history of sudden death
Preexcitation syndromes
Brugada pattern on ECG
Palpitations at time of syncope
Syncope at rest or during exercise

Abbreviations: ECG, electrocardiogram.

I-54. The answer is C. *(Chap. 19)* This patient presents with vestibular neuritis, possibly due to herpes zoster. The vesicular lesions on the ear shown in this case are suggestive of herpes zoster oticus. Most patients with vestibular neuritis recover spontaneously, but glucocorticoids can improve outcome if administered within 3 days of symptom onset. Antiviral medications are of no proven benefit and are not typically given unless there is evidence to suggest herpes zoster oticus (Ramsay Hunt syndrome) as in this case. Vestibular suppressant medications may reduce acute symptoms but should be avoided after the first several days because they may impede central compensation and recovery. Patients should be encouraged to resume a normal level of activity as soon as possible, and directed vestibular rehabilitation therapy may accelerate improvement. There is no suggestion of an ischemic stroke, which would warrant thrombolytic therapy.

I-55. The answer is E. *(Chap. 19)* Vertigo describes a perceived sense of spinning or other motion. Vestibular causes of vertigo may be caused by peripheral lesions affecting the labyrinths or the vestibular nerves, or caused by disease in the central vestibular pathways. Peripheral lesions usually present with unidirectional horizontal nystagmus. Although conjugate horizontal jerk nystagmus may be seen in either peripheral or central causes of vertigo, all of the other forms of nystagmus implicate a central etiology. Downbeat nystagmus is a pure vertical nystagmus associated with cerebellar disease. Gaze-evoked nystagmus describes nystagmus that changes direction with gaze. It is characteristic of cerebellar disease. Rebound nystagmus is a type of primary position nystagmus provoked by eccentric gaze. It is found in cerebellar or brainstem disease. Pure torsional nystagmus is also a central sign.

I-56. **The answer is C.** *(Chap. 19)* Bilateral defects in the vestibular system can cause both imbalance and oscillopsia. The head impulse test is a bedside assessment of the vestibulo-ocular reflex (VOR) used to assess vestibular hypofunction. In the test, the patient fixates on a target while the examiner rapidly rotates the head. When the VOR is intact, a patient is able to maintain focused gaze despite head movements to the side. When the VOR is deficient, the eyes deviate with the head movement, and a corrective saccade opposite in direction to the head movement returns the eyes to the focus point. In this case, injury to the peripheral vestibular system is suggested by the bilaterally abnormal head impulse test. All aminoglycosides, including gentamicin, are associated with vestibular toxicity.

I-57. **The answer is E.** *(Chap. 20)* Fatigue describes the near universal human experience of weariness or exhaustion. Fatigue may be a nonspecific manifestation of psychiatric disease, neurologic disease, sleep disorders, endocrine disorders, kidney or liver disease, rheumatologic disorders, infection, malignancy, anemia, obesity, malnutrition, pregnancy, or diseases of unclear cause. A suggested approach to screening includes a complete blood count with differential, electrolytes, glucose, renal function, liver function, and thyroid function tests. Testing for HIV and adrenal function can also be considered. However, extensive laboratory testing infrequently identifies the cause of chronic fatigue and may more often lead to false-positive findings and prolonged workups. Because low-titer positive antinuclear antibodies (ANAs) are not uncommon in otherwise healthy adults, ANA testing is unlikely to be helpful in isolation. Electromyography with nerve conduction studies may have a role if the presence of muscle weakness cannot be determined by physical examination. Testing for viral or bacterial infections is often unhelpful. Although complete resolution of fatigue is uncommon, longitudinal and multidisciplinary follow-up sometimes identifies a previously undiagnosed serious cause of chronic fatigue.

I-58, I-59, and I-60. **The answers are A, C, and B, respectively.** *(Chap. 21)* Lesions of the upper motor neurons or their descending axons to the spinal cord (Figure I-60A) produce weakness through decreased activation of lower motor neurons. In general, distal muscle groups are affected more severely than proximal ones, and axial movements are spared unless the lesion is severe and bilateral. Spasticity is typical but may not be present acutely. Psychogenic weakness may occur without a recognizable organic basis. It tends to be variable, inconsistent, and with a pattern of distribution that cannot be explained on a neuroanatomic basis. On formal testing, antagonists may contract when the patient is supposedly activating the agonist muscle. The severity of weakness is out of keeping with the patient's daily activities. Myopathic weakness is produced by a decrease in the number or contractile force of muscle fibers activated within motor units. With muscular dystrophies, inflammatory myopathies, or myopathies with muscle fiber necrosis, the number of muscle fibers is reduced within many motor units. On electromyogram, the size of each motor unit action potential is decreased, and motor units must be recruited more rapidly than normal to produce the desired power. Some myopathies produce weakness through loss of contractile force of muscle fibers or through relatively selective involvement of type 2 (fast) fibers. These myopathies may not affect the size of individual motor unit action potentials and are detected by a discrepancy between the electrical activity and force of a muscle. Lower motor neuron weakness pattern results from disorders of lower motor neurons in the brainstem motor nuclei and the anterior horn of the spinal cord or from dysfunction of the axons of these neurons as they pass to skeletal muscle (Figure I-60B). Weakness is due to a decrease in the number of muscle fibers that can be activated through a loss of motor neurons or disruption of their connections to muscle. Loss of γ motor neurons does not cause weakness but decreases tension on the muscle spindles, which decreases muscle tone and attenuates the stretch reflexes. An absent stretch reflex suggests involvement of spindle afferent fibers (Table I-60).

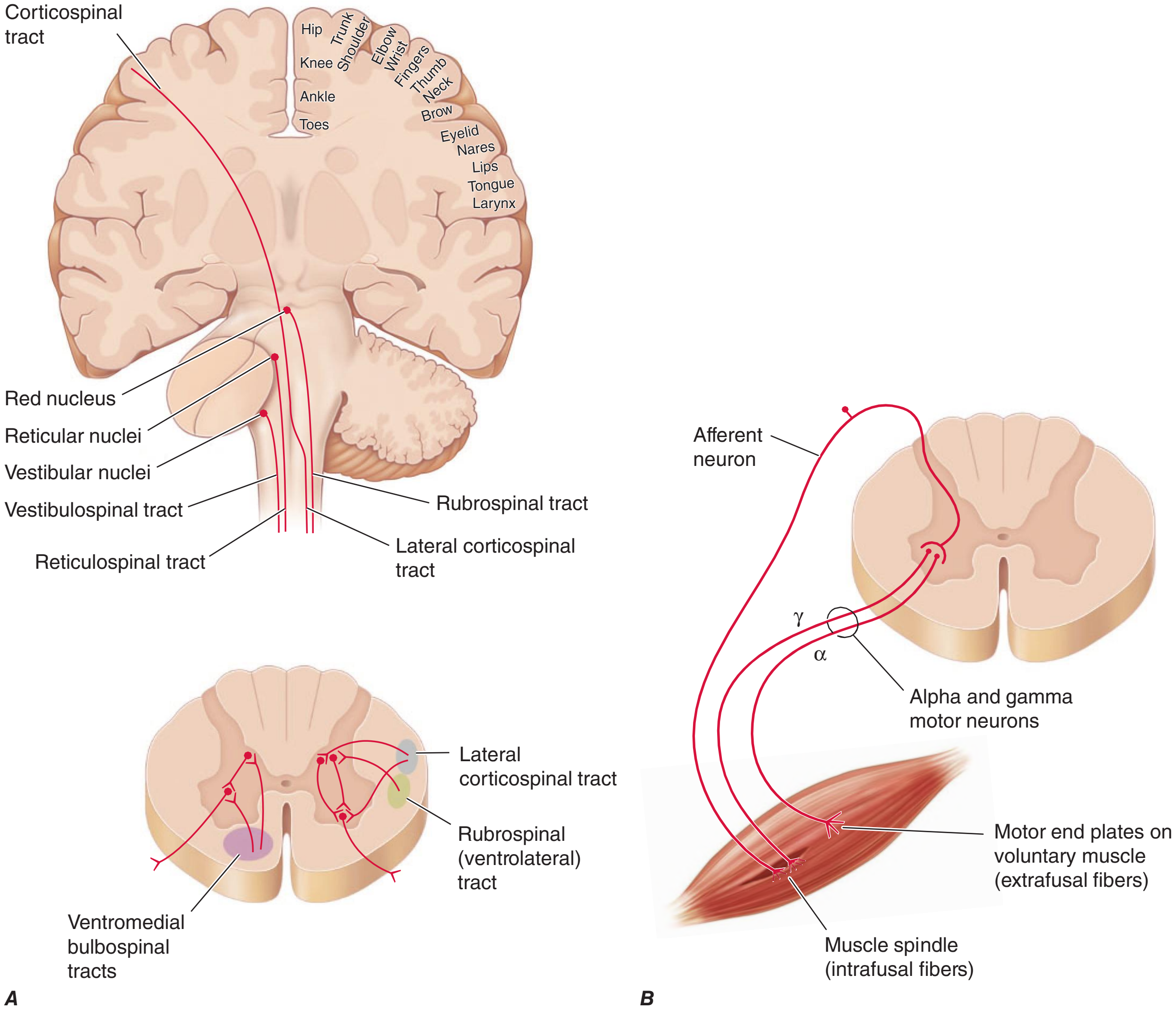

Corticospinal tract
Hip
Trunk
Shoulder
Elbow
Wrist
Fingers
Thumb
Neck
Brow
Eyelid
Nares
Lips
Tongue
Larynx
Knee
Ankle
Toes
Red nucleus
Reticular nuclei
Vestibular nuclei
Vestibulospinal tract
Reticulospinal tract
Rubrospinal tract
Lateral corticospinal tract
Lateral corticospinal tract
Rubrospinal (ventrolateral) tract
Ventromedial bulbospinal tracts
A
Afferent neuron
γ
α
Alpha and gamma motor neurons
Motor end plates on voluntary muscle (extrafusal fibers)
Muscle spindle (intrafusal fibers)
B

FIGURE I-60

TABLE I-60 Causes of Episodic Generalized Weakness

1. Electrolyte disturbances, e.g., hypokalemia, hyperkalemia, hypercalcemia, hypernatremia, hyponatremia, hypophosphatemia, hypermagnesemia
2. Muscle disorders
   a. Channelopathies (periodic paralyses)
   b. Metabolic defects of muscle (impaired carbohydrate or fatty acid utilization; abnormal mitochondrial function)
3. Neuromuscular junction disorders
   a. Myasthenia gravis
   b. Lambert-Eaton myasthenic syndrome
4. Central nervous system disorders
   a. Transient ischemic attacks of the brainstem
   b. Transient global cerebral ischemia
   c. Multiple sclerosis
5. Lack of voluntary effort
   a. Anxiety
   b. Pain or discomfort
   c. Somatization disorder

I-61. **The answer is D.** *(Chap. 21)* Complaints of weakness in a patient have a multitude of causes, and it is important to perform a thorough history and physical examination to help localize the site of weakness. Lower motor neuron diseases occur when there is destruction of the cell bodies of the lower motor neurons in the brainstem or the anterior horn of the spinal cord. Lower motor neuron diseases can also occur due to direct axonal dysfunction and demyelination. The primary presenting symptoms are those of distal muscle weakness such as tripping or decreased handgrip strength. When a motor neuron becomes diseased, it may discharge spontaneously, leading to muscle fasciculations that are not seen in disease of the upper motor neurons or myopathies. Additionally, on physical examination, lower motor neuron disease leads to decreases in muscle tone and decreased or absent deep tendon reflexes. Over time, severe muscle atrophy can occur. A Babinski sign should not be present. If there is evidence of a Babinski sign in the presence of lower motor neuron disease, this should raise the suspicion of a disorder affecting both upper and lower motor neurons such as amyotrophic lateral sclerosis.

I-62. **The answer is A.** *(Chap. 22)* Crossed patterns of sensory disturbance, in which one side of the face and the opposite side of the body are affected, localize to the lateral medulla (Figure I-62). Here a small lesion may damage both the ipsilateral descending trigeminal tract and the ascending spinothalamic fibers subserving the opposite arm, leg, and hemitorso. A lesion in the tegmentum of the pons and midbrain, where the lemniscal and spinothalamic tracts merge, causes pansensory loss contralaterally. Hemisensory disturbance with tingling numbness from head to foot is often thalamic in origin but also can arise from the anterior parietal region. With lesions of the parietal lobe involving either the cortex or the subjacent white matter, the most prominent symptoms are contralateral hemineglect, hemi-inattention, and a tendency not to use the affected hand and arm. On cortical sensory testing (e.g., two-point discrimination, graphesthesia), abnormalities are often found but primary sensation is usually intact. If the spinal cord is transected, all sensation is lost below the level of transection. Bladder and bowel function also are lost, as is motor function.

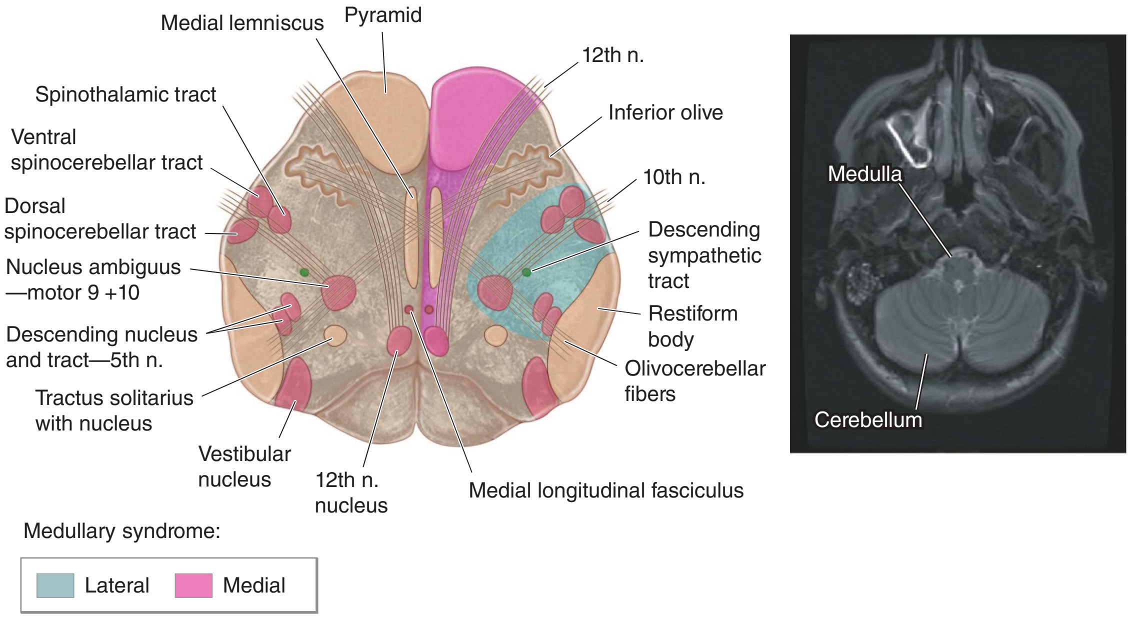

Medial lemniscus
Pyramid
12th n.
Spinothalamic tract
Inferior olive
Ventral spinocerebellar tract
10th n.
Dorsal spinocerebellar tract
Descending sympathetic tract
Nucleus ambiguus —motor 9 +10
Restiform body
Descending nucleus and tract—5th n.
Olivocerebellar fibers
Tractus solitarius with nucleus
Vestibular nucleus
12th n. nucleus
Medial longitudinal fasciculus
Medullary syndrome:
Lateral
Medial
Medulla
Cerebellum

FIGURE I-62

I-63. **The answer is C.** *(Chap. 22)* In focal nerve trunk lesions, sensory abnormalities are readily mapped and generally have discrete boundaries (Figure I-63). Root ("radicular") lesions frequently are accompanied by deep, aching pain along the course of the related nerve trunk. With compression of a fifth lumbar (L5) or first sacral (S1) root, as from a ruptured intervertebral disk, sciatica (radicular pain relating to the sciatic nerve trunk) is a common manifestation. With a lesion affecting a single root, sensory deficits may be minimal

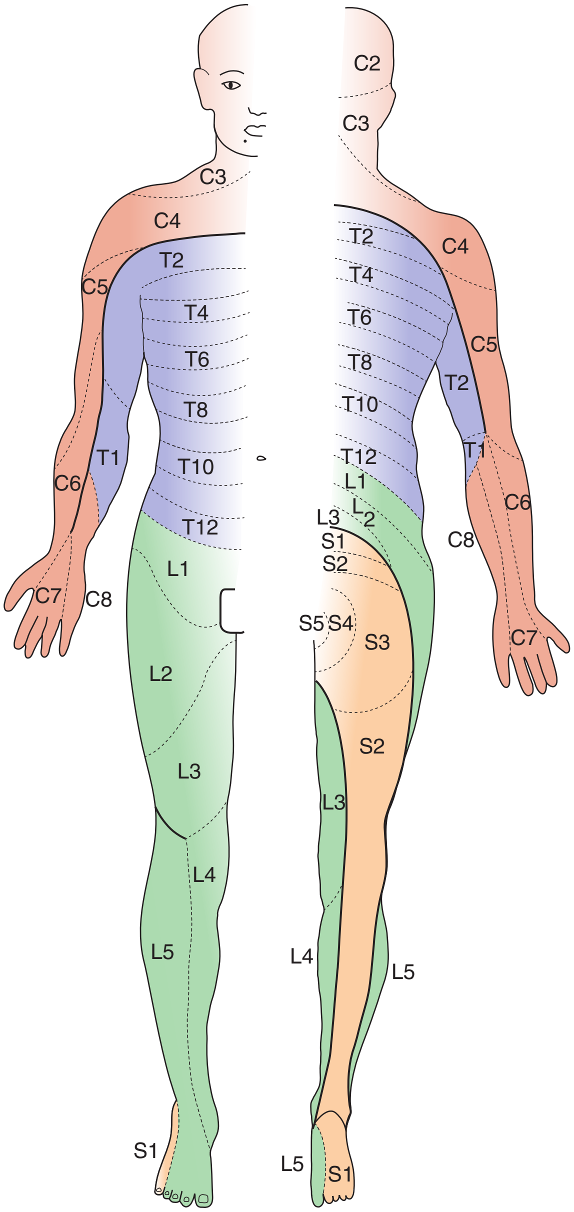


FIGURE I-63 Reproduced from Sinclair D: *Mechanisms of Cutaneous Sensation*. Oxford, UK: Oxford University Press, 1981. Used with permission from Dr. David Sinclair.

or absent because adjacent root territories overlap extensively. Isolated mononeuropathies may cause symptoms beyond the territory supplied by the affected nerve, but abnormalities on examination typically are confined to appropriate anatomic boundaries. The lower medial leg is supplied by the L4 nerve root and is therefore the most likely cause of this person's pain.

I-64. **The answer is D.** *(Chap. 22)* Cutaneous sensory receptors are classified by the type of stimulus that optimally excites them. They consist of naked nerve endings (nociceptors, which respond to tissue-damaging stimuli, and thermoreceptors, which respond to noninjurious thermal stimuli) and encapsulated terminals (several types of mechanoreceptor, activated by physical deformation of the skin). Each type of receptor has its own set of sensitivities to specific stimuli, size, and distinctness of receptive fields, and adaptational qualities. Afferent fibers in peripheral nerve trunks traverse the dorsal roots and enter the dorsal horn of the spinal cord. From there, the polysynaptic projections of the smaller fibers (unmyelinated and small myelinated), which subserve mainly nociception, itch, temperature sensibility, and touch, cross and ascend in the opposite anterior and lateral columns of the spinal cord, through the brainstem, to the ventral posterolateral (VPL) nucleus of the thalamus and ultimately project to the postcentral gyrus of the parietal cortex. This is the spinothalamic pathway or anterolateral system. The larger fibers, which subserve tactile and position sense and kinesthesia, project rostrally in the posterior and posterolateral columns on the same side of the spinal cord and make their first synapse in the gracile or cuneate nucleus of the lower medulla. Axons of second-order neurons decussate and ascend in the medial lemniscus located medially in the medulla and in the tegmentum of the pons and midbrain and synapse in the VPL nucleus; third-order neurons project to parietal cortex as well as to other cortical areas. This large-fiber system is referred to as the posterior column–medial lemniscal pathway (lemniscal, for short). Although the fiber types and functions that make up the spinothalamic and lemniscal systems are relatively well known, many other fibers, particularly those associated with touch, pressure, and position sense, ascend in a diffusely distributed pattern both ipsilaterally and contralaterally in the anterolateral quadrants of the spinal cord. This explains why a complete lesion of the posterior columns of the spinal cord may be associated with little sensory deficit on examination. Nerve conduction studies and nerve biopsy are important means of investigating the peripheral nervous system, but they do not evaluate the function or structure of cutaneous receptors and free nerve endings or of unmyelinated or thinly myelinated nerve fibers in the nerve trunks. Skin biopsy can be used to evaluate these structures in the dermis and epidermis.

I-65. **The answer is C.** *(Chap. 23)* Risk factors for falls may be *intrinsic* (e.g., gait and balance disorders) or *extrinsic* (e.g., polypharmacy, and environmental factors); some risk factors are modifiable. The presence of multiple risk factors is associated with a substantially increased risk of falls. Table I-65 summarizes a meta-analysis of studies establishing the principal risk factors for falls. Polypharmacy (use of four or more prescription medications) has also been identified as an important risk factor. All of the answers listed are associated with an increased risk of falls. However, muscle weakness has been associated with the greatest increased risk of falls.

TABLE I-65 Meta-Analysis of Risk Factors for Falls in Older Persons

Risk Factor	Mean RR (OR)	Range
Muscle weakness	4.4	1.5–10.3
History of falls	3.0	1.7–7.0
Gait deficit	2.9	1.3–5.6
Balance deficit	2.9	1.6–5.4
Use assistive device	2.6	1.2–4.6
Visual deficit	2.5	1.6–3.5
Arthritis	2.4	1.9–2.9
Impaired ADL	2.3	1.5–3.1
Depression	2.2	1.7–2.5
Cognitive impairment	1.8	1.0–2.3
Age >80 years	1.7	1.1–2.5

Abbreviations: ADL, activity of daily living; OR, odds ratio from retrospective studies; RR, relative risk from prospective studies.
Source: Adapted with permission from Guideline for the prevention of falls in older persons. American Geriatrics Society, British Geriatrics Society, and American Academy of Orthopaedic Surgeons Panel on Falls Prevention. *J Am Geriatr Soc* 49:664, 2001.

I-66. **The answer is B.** *(Chap. 23)* Characteristics on neurologic examination can assist with the localization of disease in gait disorders. In this case, the patient presents with signs of a frontal gait disorder or parkinsonism. The specific characteristics that would be seen with a frontal gait disorder are a wide-based stance with slow and short shuffling steps. The patient may have difficulty rising from a chair and has a slow hesitating start. Likewise, there is great difficulty with turning, with multiple steps required to complete a turn. The patient has very significant postural instability. However, cerebellar signs are typically absent. Romberg sign may or may not be positive, and seated cerebellar testing is normal, including heel-to-shin testing and rapid alternating movements. Additionally, there should otherwise be normal muscle bulk and tone without sensory or strength deficits.

The most common cause of frontal gait disorders (sometimes known as gait apraxia) is cerebrovascular disease, especially small-vessel subcortical disease. Communicating hydrocephalus also presents with a gait disorder of this type. In some individuals, the gait disorder precedes other typical symptoms such as incontinence or mental status change. Alcoholic cerebellar degeneration and multiple system atrophy present with signs of cerebellar ataxia. Characteristics of cerebellar ataxia include wide-based gait with variable velocity. Gait initiation is normal, but the patient is hesitant during turns. The stride is lurching and irregular. Falls are a late event. The heel-to-shin test is abnormal and the Romberg sign is variably positive. Neurosyphilis and lumbar myelopathy are examples of sensory ataxia. Sensory ataxia presents with frequent falls. The gait with sensory ataxia, however, is narrow based. Often the patient is noted to be looking down while walking. The patient tends to walk slowly but has path deviation. Gait is initiated normally, but the patient may have some difficulty with turning. The Romberg is typically unsteady and may result in falls.

I-67. **The answer is B.** *(Chap. 24)* Management of delirium begins with treatment of the underlying inciting factor (e.g., patients with systemic infections should be given appropriate antibiotics). These treatments often lead to prompt resolution of delirium. Relatively simple methods of supportive care can be highly effective. Reorientation by the nursing staff and family combined with visible clocks, calendars, and outside-facing windows can reduce confusion. Sensory isolation should be prevented by providing glasses and hearing aids to patients who need them. Sundowning can be addressed to a large extent through vigilance to appropriate sleep-wake cycles. Simple standard nursing practices such as maintaining proper nutrition and volume status as well as managing pain, incontinence, and skin breakdown also help alleviate discomfort and resulting confusion. In this patient with an infection and nephrolithiasis, antibiotic therapy and pain management will be important. Chemical restraints should be avoided, but when necessary, very-low-dose typical or atypical antipsychotic medications administered on an as-needed basis can be used; however, trials show that these medications are ineffective in treating delirium; therefore, they should be reserved for patients who display severe agitation and significant potential to harm themselves or staff. The recent association of antipsychotic use in the elderly with increased mortality rates underscores the importance of using these medications judiciously and only as a last resort. Benzodiazepines often worsen confusion through their sedative properties. Although many clinicians still use benzodiazepines to treat acute confusion, their use should be limited to cases in which delirium is caused by alcohol or benzodiazepine withdrawal.

I-68. **The answer is E.** *(Chap. 24)* This patient is presenting with intensive care unit (ICU) delirium. Because the diagnosis of delirium is clinical and is made at the bedside, a careful history and physical examination are necessary in evaluating patients with possible confusional states. Screening tools can aid physicians and nurses in identifying patients with delirium, including the Confusion Assessment Method (CAM; Table I-68); the Nursing Delirium Screening Scale (NuDESC); the Organic Brain Syndrome Scale; the Delirium Rating Scale; and, in the ICU, the ICU version of the CAM and the Delirium Detection Score. Using the well-validated CAM, a diagnosis of delirium is made if there is (1) an acute onset and fluctuating course and (2) inattention accompanied by either (3) disorganized thinking or (4) an altered level of consciousness. The causes of delirium are many. No definitive algorithm applies to all cases. The etiology of delirium is best determined in a stepwise approach that begins with a careful history and physical examination with special attention to medication history including over-the-counter medications, herbals, and drugs of abuse. Metabolic abnormalities such as electrolyte disturbances of sodium, calcium, magnesium, or glucose can cause delirium, and mild derangements can lead to substantial cognitive disturbances in susceptible individuals. Other common metabolic etiologies include liver and renal failure, hypercarbia and hypoxemia, vitamin deficiencies of thiamine and B_{12}, autoimmune disorders including central nervous system vasculitis, and endocrinopathies such as thyroid and adrenal disorders. It is reasonable to screen basic laboratories including a complete blood count; electrolyte panel including calcium, magnesium, phosphorus, and glucose; and liver and renal function tests in the initial evaluation of delirium. Alterations in serum electrolytes such as sodium, potassium, bicarbonate, calcium, magnesium, and phosphorus may contribute or cause delirium.

TABLE I-68 The Confusion Assessment Method (CAM) Diagnostic Algorithm[a]

The diagnosis of delirium requires the presence of features 1 and 2 **and** *either* feature 3 or 4.

Feature 1. Acute Onset and Fluctuating Course

This feature is satisfied by positive responses to the following questions: Is there evidence of an acute change in mental status from the patient's baseline? Did the (abnormal) behavior fluctuate during the day, that is, tend to come and go, or did it increase and decrease in severity?

Feature 2. Inattention

This feature is satisfied by a positive response to the following question: Did the patient have difficulty focusing attention, for example, being easily distractible, or have difficulty keeping track of what was being said?

Feature 3. Disorganized Thinking

This feature is satisfied by a positive response to the following question: Was the patient's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?

Feature 4. Altered Level of Consciousness

This feature is satisfied by any answer other than "alert" to the following question: Overall, how would you rate the patient's level of consciousness: alert (normal), vigilant (hyperalert), lethargic (drowsy, easily aroused), stupor (difficult to arouse), or coma (unarousable)?

[a] Information is usually obtained from a reliable reporter, such as a family member, caregiver, or nurse.
Source: Reproduced with permission from Inouye SK et al: Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med* 113:941, 1990.

Especially in the elderly, screening for systemic infection with urinalysis, cultures, and chest imaging is important. In younger patients, toxicology may be appropriate earlier in the workup. Guided by the initial evaluation, further evaluation may include additional testing for systemic infections, other toxic/metabolic etiologies, ischemia, vitamin deficiencies, endocrinopathies, autoimmune disorders, neoplastic disorders, cerebrovascular disorders, or seizure-related disorders. Although screening for vitamin B_{12} deficiency, syphilis, or hyperammonemia may have a role in the subsequent evaluation of delirium, these tests are not routinely recommended in the initial evaluation. Brain imaging in delirium is often unhelpful but may be considered if the initial evaluation is unrevealing.

I-69. **The answer is A.** *(Chap. 24)* Delirium is an acute and fluctuating decline in cognition typified by inattention, disorganized thinking, and an altered level of consciousness. The common etiologies of delirium are manifold, and in many patients, the cause is multifactorial. Nearly one-third of cases of delirium are due to medications. Especially in older adults, drugs with anticholinergic properties may precipitate delirium. Deficiency of acetylcholine may play a key role in the pathogenesis of delirium. Diphenhydramine is a sedating antihistamine with substantial anticholinergic activity. Diphenhydramine does not significantly antagonize the activity of serotonin, dopamine, or norepinephrine.

I-70. **The answer is B.** *(Chaps. 25 and 424)* This patient's presentation is typical of Alzheimer's dementia (AD). In AD, the early deficits involve episodic memory, category generation ("name as many animals as you can in 1 minute"), and visuoconstructive ability. Usually deficits in verbal or visual episodic memory are the first neuropsychological abnormalities detected, and tasks that require the patient to recall a long list of words or a series of pictures after a predetermined delay will demonstrate deficits in most patients. Typical AD spares motor systems until later in the course. Support for the diagnosis of AD includes hippocampal atrophy in addition to posterior-predominant cortical atrophy. Focal frontal, insular, and/or anterior temporal atrophy suggests frontotemporal dementia. Dementia with Lewy bodies often features less prominent atrophy, with greater involvement of amygdala than hippocampus. In Creutzfeldt-Jakob Disease, magnetic resonance diffusion-weighted imaging reveals restricted diffusion within the cortical ribbon and/or basal ganglia in most patients. Extensive multifocal white matter abnormalities suggest a vascular etiology. Communicating hydrocephalus with vertex effacement (crowding of dorsal

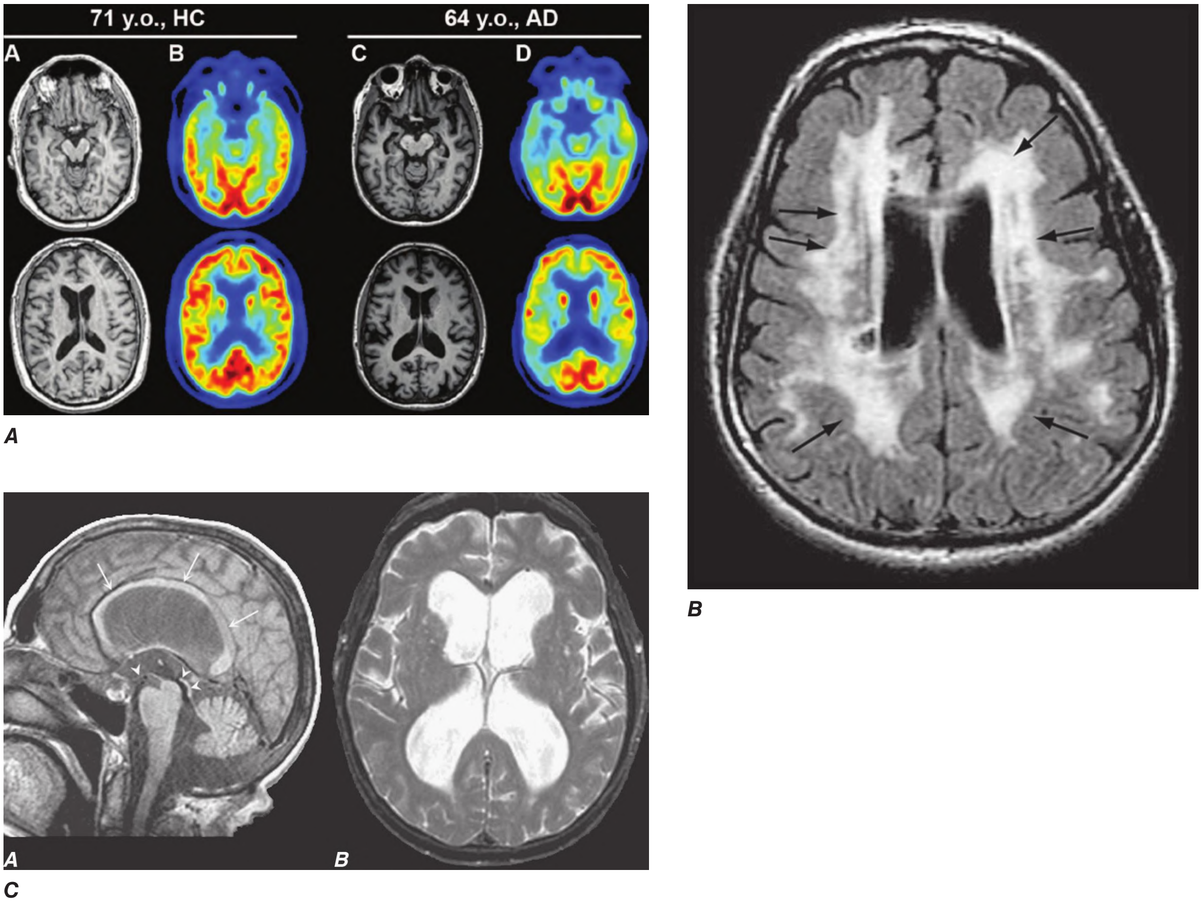


FIGURE I-70 **A,** Alzheimer's disease (AD). Axial T1-weighted MRI of a healthy 71-year-old (***A***) and a 64-year-old with AD (***C***). Note the reduction in medial temporal lobe volume in the patient with AD. Fluorodeoxyglucose positron emission tomography scans of the same individuals (***B*** and ***D***) demonstrate reduced glucose metabolism in the posterior temporoparietal regions bilaterally in AD, a typical finding in this condition. HC, healthy control. **B,** Diffuse white matter disease. Axial fluid-attenuated inversion recovery (FLAIR) MRI through the lateral ventricles reveals multiple areas of hyperintensity (*arrows*) involving the periventricular white matter as well as the corona radiata and striatum. Although seen in some individuals with normal cognition, this appearance is more pronounced in patients with dementia of a vascular etiology. **C,** Normal-pressure hydrocephalus. (***A***) Sagittal T1-weighted MRI demonstrates dilation of the lateral ventricle and stretching of the corpus callosum (*arrows*), depression of the floor of the third ventricle (*single arrowhead*), and enlargement of the aqueduct (*double arrowhead*). Note the diffuse dilation of the lateral, third, and fourth ventricles with a patent aqueduct, typical of communicating hydrocephalus. (***B***) Axial T2-weighted MRIs demonstrate dilation of the lateral ventricles. This patient underwent successful ventriculoperitoneal shunting. (Used with permission from Gil Rabinovici, University of California, San Francisco and William Jagust, University of California, Berkeley.)

convexity gyri/sulci), gaping Sylvian fissures despite minimal cortical atrophy, and additional features shown in Figure I-70, parts A–C, suggest normal pressure hydrocephalus.

I-71. **The answer is C.** *(Chap. 25)* Subtle cumulative decline in episodic memory is a common part of aging. This frustrating experience, often the source of jokes and humor, is often referred to as *benign forgetfulness of the elderly*. *Benign* means that it is not so progressive or serious that it impairs reasonably successful and productive daily functioning, although the distinction between benign and more significant memory loss can be difficult to make. At age 85, the average person is able to learn and recall approximately one-half of the items (e.g., words on a list) that he or she could at age 18. A measurable cognitive problem that does not seriously disrupt daily activities is often referred to as *mild cognitive impairment* (MCI). Factors that predict progression from MCI to an Alzheimer's disease (AD) dementia include a prominent memory deficit, family history of dementia, presence of an apolipoprotein ε4 (Apo ε4) allele, small hippocampal volumes, an AD-like signature of cortical atrophy, low cerebrospinal fluid Aβ, and elevated tau or evidence of brain amyloid deposition on positron emission tomography (PET) imaging. α-Synuclein neuronal inclusions, or Lewy bodies, are found in Lewy body dementia. Single-photon emission computed tomography (SPECT) and PET scanning show temporal-parietal hypoperfusion or hypometabolism in Alzheimer's dementia and frontotemporal deficits in frontotemporal dementia.

I-72. **The answer is D.** *(Chap. 25)* Based on initial symptoms, mental status, neuropsychiatric evaluation, neurologic examination, and imaging, it is often possible to differentiate the major causes of dementia as listed in Table I-72. In this case, the combination of apathy, poor judgment, disinhibition, and overeating makes frontotemporal dementia the most likely diagnosis.

TABLE I-72 Clinical Differentiation of the Major Dementias

Disease	First Symptom	Mental Status	Neuropsychiatry	Neurology	Imaging
AD	Memory loss	Episodic memory loss	Irritability, anxiety, depression	Initially normal	Entorhinal cortex and hippocampal atrophy
FTD	Apathy; poor judgment/insight, speech/language; hyperorality	Frontal/executive and/or language; spares drawing	Apathy, disinhibition, overeating, compulsivity	May have vertical gaze palsy, axial rigidity, dystonia, alien hand, or MND	Frontal, insular, and/or temporal atrophy; usually spares posterior parietal lobe
DLB	Visual hallucinations, REM sleep behavior disorder, delirium, Capgras syndrome, parkinsonism	Drawing and frontal/executive; spares memory; delirium-prone	Visual hallucinations, depression, sleep disorder, delusions	Parkinsonism	Posterior parietal atrophy; hippocampi larger than in AD
CJD	Dementia, mood, anxiety, movement disorders	Variable, frontal/executive, focal cortical, memory	Depression, anxiety, psychosis in some	Myoclonus, rigidity, parkinsonism	Cortical ribboning and basal ganglia or thalamus hyperintensity on diffusion/FLAIR MRI
Vascular	Often but not always sudden; variable; apathy, falls, focal weakness	Frontal/executive, cognitive slowing; can spare memory	Apathy, delusions, anxiety	Usually motor slowing, spasticity; can be normal	Cortical and/or subcortical infarctions, confluent white matter disease

Abbreviations: AD, Alzheimer's disease; CBD, cortical basal degeneration; CJD, Creutzfeldt-Jakob disease; DLB, dementia with Lewy bodies; FLAIR, fluid-attenuated inversion recovery; FTD, frontotemporal dementia; MND, motor neuron disease; MRI, magnetic resonance imaging; REM, rapid eye movement.

I-73. **The answer is B.** *(Chap. 25)* Approximately 10% of all persons over the age of 70 have significant memory loss, and in more than half, the cause is Alzheimer's disease (AD). AD can occur in any decade of adulthood, but it is the most common cause of dementia in the elderly. AD most often presents with an insidious onset of memory loss followed by a slowly progressive dementia over several years. Pathologically, atrophy is distributed throughout the medial temporal lobes, as well as lateral and medial parietal lobes and lateral frontal cortex. Microscopically, there are neurofibrillary tangles composed of hyperphosphorylated tau filaments, and accumulation of amyloid in blood vessel walls in cortex and leptomeninges. The cognitive changes of AD tend to follow a characteristic pattern, beginning with memory impairment and spreading to language and visuospatial deficits. Yet, approximately 20% of patients with AD present with nonmemory complaints such as word-finding, organizational, or navigational difficulty. In the early stages of the disease, the memory loss may go unrecognized or be ascribed to benign forgetfulness. Slowly the cognitive problems begin to interfere with daily activities, such as keeping track of finances, following instructions on the job, driving, shopping, and housekeeping. Some patients are unaware of these difficulties (*anosognosia*), whereas others remain acutely attuned to their deficits. Social graces, routine behavior, and superficial conversation may be surprisingly intact. Language becomes impaired—first naming, then comprehension, and finally fluency. In some patients, *aphasia* is an early and prominent feature. Word-finding difficulties and circumlocution may be a problem even when formal testing demonstrates intact naming and fluency. Visuospatial deficits begin to interfere with dressing, eating, or even walking, and patients fail to solve simple puzzles or copy geometric figures. Simple calculations and clock reading become difficult in parallel. Loss of judgment and reasoning is inevitable. Delusions are common and usually simple, with common themes of theft, infidelity, or misidentification. In end-stage AD, patients become rigid, mute, incontinent, and bedridden. Hyperactive tendon reflexes and myoclonic jerks may occur spontaneously or in response to physical or auditory stimulation. Generalized seizures may also occur. Often death results from malnutrition, secondary infections, pulmonary emboli, heart disease, or, most commonly, aspiration. The typical duration of AD is 8–10 years, but the course can range from 1 to 25 years. For unknown reasons, some AD patients show a steady decline in function, while others have prolonged plateaus without major deterioration.

I-74. **The answer is A.** *(Chap. 26)* The lesion site most commonly associated with Wernicke aphasia caused by cerebrovascular accidents is the posterior portion of the language network. An embolus to the inferior division of the middle cerebral artery, to the posterior temporal or angular branches in particular, is the most common etiology. Wernicke aphasia is when comprehension, repetition, and naming are impaired but fluency is preserved. Option B describes Broca aphasia, option C is global aphasia, and option D is conduction aphasia (Table I-74).

TABLE I-74 Clinical Features of Aphasias and Related Conditions Commonly Seen in Cerebrovascular Accidents

	Comprehension	Repetition of Spoken Language	Naming	Fluency
Wernicke	Impaired	Impaired	Impaired	Preserved or increased
Broca	Preserved (except grammar)	Impaired	Impaired	Decreased
Global	Impaired	Impaired	Impaired	Decreased
Conduction	Preserved	Impaired	Impaired	Preserved
Nonfluent (anterior) transcortical	Preserved	Preserved	Impaired	Impaired
Fluent (posterior) transcortical	Impaired	Preserved	Impaired	Preserved
Isolation	Impaired	Echolalia	Impaired	No purposeful speech
Anomic	Preserved	Preserved	Impaired	Preserved except for word-finding pauses
Pure word deafness	Impaired only for spoken language	Impaired	Preserved	Preserved
Pure alexia	Impaired only for reading	Preserved	Preserved	Preserved

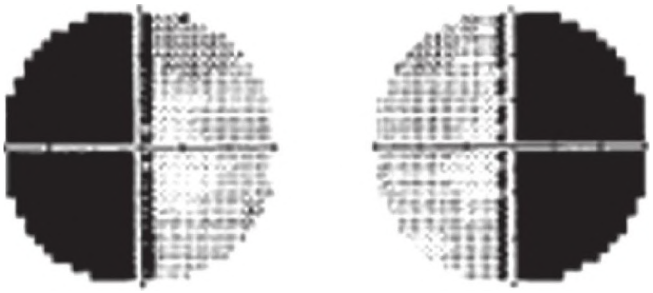
I-75. **The answer is C.** *(Chap. 25)* The parietofrontal area of the brain is responsible for spatial orientation. The major components of the network include the cingulate cortex, posterior parietal cortex, and the frontal eye fields. In addition, subcortical areas in the striatum and thalamus are also important. Together, these systems integrate information to maintain spatial cognition, and a lesion in any of these areas can lead to hemispatial neglect. In neglect syndromes, three behavioral manifestations are seen: sensory events in the neglected hemisphere have less overall impact, there is a paucity of conscious acts directed toward the neglected hemisphere, and the patient behaves as if the neglected hemisphere is devalued. In Figure I-75, almost all of the As (the target) represented on the left half of the figure are missed. This is an example of a target detection task. Hemianopia alone is not sufficient to cause this finding because the individual can turn his or her head left and right to identify the targets. Bilateral disorders of the parietofrontal area of the brain can lead to severe spatial disorientation known as Balint syndrome. In Balint syndrome, there is inability to orderly scan the environment (oculomotor apraxia) and inaccurate manual reaching for objects (optic apraxia). A third finding in Balint syndrome is simultanagnosia. Simultanagnosia refers to the inability to integrate information in the center of the gaze with peripheral information. An example would be a target detection test where only the As present in the outer portion of the figure would be indicated. Individuals with this finding also tend to miss the larger objects in a figure and would not be able to accurately identify the target when it was made much larger than the surrounding letters. Construction apraxia refers to the inability to copy a simple line drawing like a house or star and occurs most commonly in association with parietal lesions. Object agnosia refers to the inability to name a generic object or describe its use, in contrast to anomia, where an individual should be able to describe the use of the object even if it cannot be named. The defect in the object agnosia is usually in the territory of the bilateral posterior cerebral arteries.

I-76. **The answer is E.** *(Chap. 28)* This is a classic representation of a left relative afferent pupillary defect, or the Marcus Gunn pupil. In this case, the left eye does not perceive the light stimulus as strongly. Thus, when the light is shined in the left eye, the bilateral constriction stimulus is less than when the light is shined in the right eye. This finding is sometimes the only clue to the presence of an optic neuritis, which can subsequently uncover a neurodemyelinating disease. The patient has equally sized pupils in dim light, ruling out Adie tonic pupil, where anisocoria is present due to parasympathetic denervation of the iris ciliary muscle in the affected eye. Thus, the anisocoria would worsen in bright light (the affected eye would be unable to constrict). Curiously, while the pupillary response to light in this condition is poor, the response to near stimulus is often relatively preserved. This can be due to oculomotor nerve palsy or be idiopathic. A similar light–near dissociation can be seen in the Argyll-Robertson pupil of neurosyphilis with involvement of the midbrain. The opposite dissociation (where a pupil reacts to light but does not accommodate to near stimulus) does not occur. Likewise, Horner syndrome would present with anisocoria with miosis (constriction) of the affected eye due to sympathetic denervation, which is not present in this patient. In this condition, the anisocoria would worsen in dim light, and the unaffected eye is free to dilate, while the affected eye is miotic. Often, concomitant ptosis and anhidrosis are seen in Horner syndrome. An optic chiasm lesion would cause a homonymous hemianopsia, which is a defect in visual fields and cannot be assessed with the swinging flashlight test. In bilateral optic neuropathy, no afferent pupil defect is present.

I-77. **The answer is E.** *(Chap. 28)* This young woman developed acute papilledema, with hemorrhages and cotton-wool spots seen on ophthalmoscopic exam. This connotes bilateral optic disc swelling from raised intracranial pressure (ICP). Headache is a common but not invariable accompaniment. Transient visual obscurations are a classic symptom of papilledema. They can occur in only one eye or simultaneously in both eyes. They usually last seconds but can persist longer. Obscurations follow abrupt shifts in posture or happen spontaneously. When obscurations are prolonged or spontaneous, the papilledema is more threatening. Visual acuity is not affected by papilledema unless the papilledema is severe, long-standing, or accompanied by macular edema and hemorrhage. Visual field testing shows enlarged blind spots and peripheral constriction. With unremitting papilledema, peripheral visual field loss progresses in an insidious fashion while the optic nerve develops atrophy. In this setting, reduction of optic disc swelling is an ominous sign of a dying nerve rather than an encouraging indication of resolving papilledema. Raised ICP is a rare side effect of tetracyclines and if it occurs, treatment consists of stopping the antibiotic and starting acetazolamide. Option A consists of treatment for migraines; however, the findings would not be expected to be present in someone having a migraine (ophthalmoscopic examination would be normal). Diabetic retinopathy (option B) is usually a late finding and would not be expected to be a presenting symptoms. Additionally, it is not expected to cause an increase in ICP. The ocular findings are proliferative diabetic retinopathy, with neovascular vessels emanating from the optic disc, or nonproliferative diabetic retinopathy, where neovascularization does not occur. In both settings one can get cotton-wool spots, hemorrhages, and exudates. Option C is suggestive of systemic infection, like endocarditis. Classical eye findings include Roth spots, which are not seen here. Option D, starting high-dose steroids, would be appropriate if this patient was suspected of having temporal arteritis. There you would also see splinter hemorrhages, visual loss, and an elevated erythrocyte sedimentation rate.

I-78. **The answer is D.** *(Chap. 28)* This girl has classic myopia, or "near-sightedness." In this condition, the globe is too long, causing light rays to be focused in front of the retina. Patients can clearly see objects near to them, but farther objects are out of focus. They require a diverging lens in front of the eye to bring objects into focus. As an alternative to eyeglasses or contact lenses, refractive error can be corrected by performing laser in situ keratomileusis (LASIK) or photorefractive keratectomy (PRK) to alter the curvature of the cornea. Emmetropia (option A) is the situation where the globe is the appropriate length and parallel rays are focused perfectly on the retina. These patients do not require corrective lenses. Hyperopia is the opposite of myopia; in this condition, the globe is too short, and light rays have a focal point "behind" the retina. These patients suffer from "far-sightedness," where objects nearby are preferentially out of focus. This condition is corrected with converging lenses in front of the eye. Presbyopia is the condition that often begins in middle age, where the lens loses refractive power, particularly for near objects, and is treated with reading glasses.

I-79. **The answer is C.** *(Chap. 28)* This patient has a classic bitemporal hemianopsia. In this condition, the nasal ganglion cells decussate to the contralateral optic tract. Decussating fibers are sensitive to pressure and thus more easily damaged. Because the nasal ganglion cells are responsible for vision in the temporal fields, damage produces a bitemporal hemianopsia. Associated conditions include pituitary lesions or other sellar lesions such as craniopharyngiomas or aneurysms. Prompt central nervous system imaging is warranted. Damage to the right retina would produce loss of vision in only the right eye. Similarly, damage to the left optic nerve would produce loss of vision in only the left eye; both of these lesions are termed "pre-chiasmatic" because they are present anterior to the optic chiasm. Right occipital lobe lesions such as a stroke would produce a homonymous hemianopsia of the left visual fields, often with macular sparing. Damage to the left parietal lobe would produce a right inferior quadrantanopsia as seen in Figure I-79, which shows the location of brain injury and resulting visual field pattern of loss.



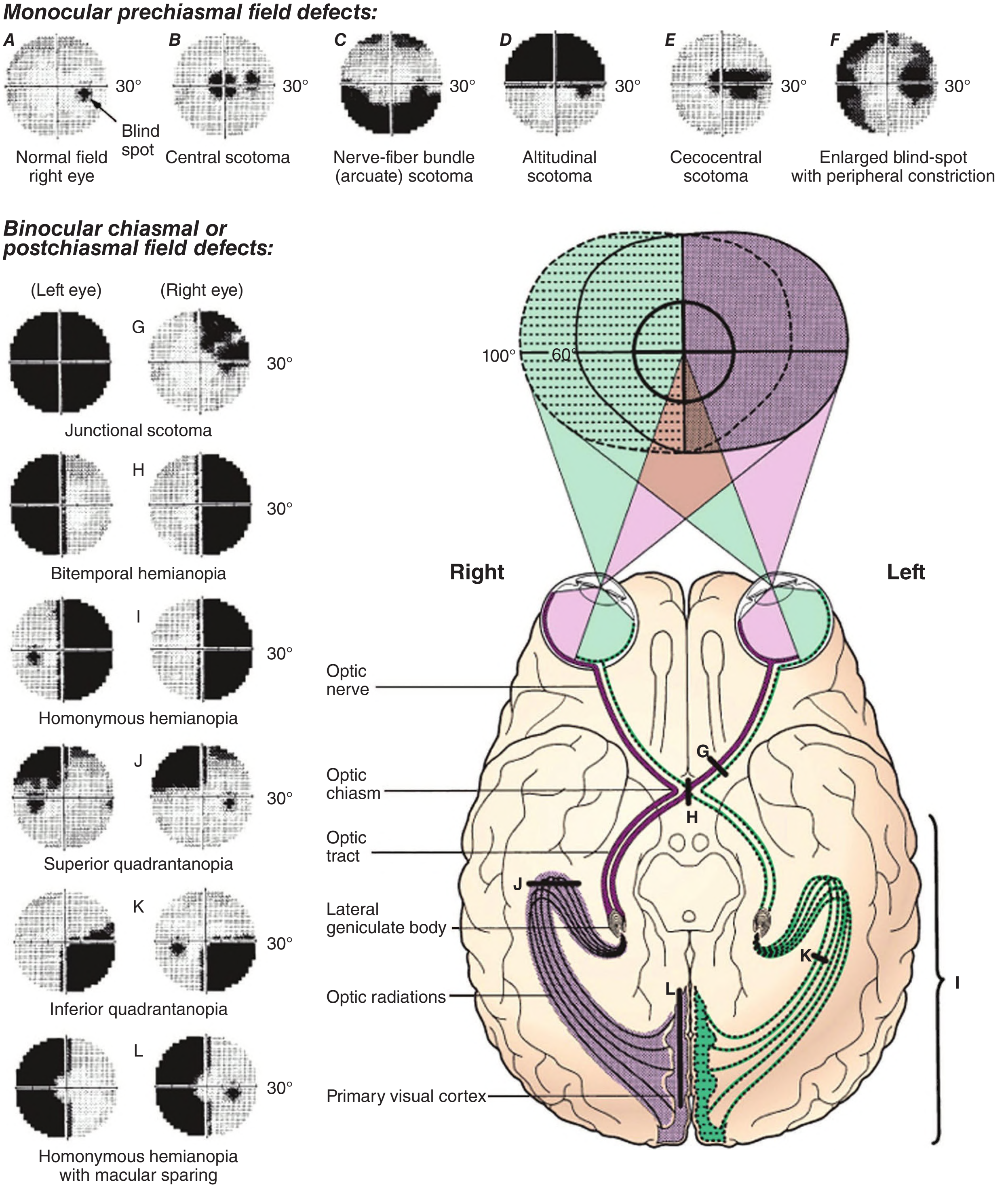

Monocular prechiasmal field defects:
A
30°
Blind spot
Normal field right eye
B
30°
Central scotoma
C
30°
Nerve-fiber bundle (arcuate) scotoma
D
30°
Altitudinal scotoma
E
30°
Cecocentral scotoma
F
30°
Enlarged blind-spot with peripheral constriction
Binocular chiasmal or postchiasmal field defects:
(Left eye)
(Right eye)
G
30°
Junctional scotoma
H
30°
Bitemporal hemianopia
I
30°
Homonymous hemianopia
J
30°
Superior quadrantanopia
K
30°
Inferior quadrantanopia
L
30°
Homonymous hemianopia with macular sparing
100°
60°
Right
Left
Optic nerve
Optic chiasm
Optic tract
Lateral geniculate body
Optic radiations
Primary visual cortex
G
H
J
K
L
I

FIGURE I-79

I-80. **The answer is C.** *(Chap. 29)* Aside from aging, the three most common identifiable causes of long-lasting or permanent loss of smell seen in the clinic are, in order of frequency, severe upper respiratory infections, head trauma, and chronic rhinosinusitis. The physiologic basis for most head trauma–related losses is the shearing and subsequent scarring of the olfactory fila as they pass from the nasal cavity into the brain cavity. Upper respiratory infections, such as those associated with the common cold, influenza, pneumonia, or HIV, can directly and permanently harm the olfactory epithelium by decreasing receptor cell number, damaging cilia on remaining receptor cells, and inducing the replacement of sensory epithelium with respiratory epithelium. The smell loss associated with chronic rhinosinusitis is related to disease severity, with most loss occurring in cases where rhinosinusitis and polyposis are both present. Interestingly, smell loss is minimal or nonexistent in progressive supranuclear palsy and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced parkinsonism. The relative contributions of disease-specific pathology or differential damage to forebrain neuromodulator/neurotransmitter systems in explaining different degrees of olfactory dysfunction among the various neurodegenerative diseases are presently unknown.

I-81. **The answer is A.** *(Chap. 29)* Olfaction is a unique sensory system in that its initial afferent projections bypass the thalamus. However, persons with damage to the thalamus can exhibit olfactory deficits, particularly ones of odor identification. Such deficits likely reflect the involvement of thalamic connections between the primary olfactory cortex and the orbitofrontal cortex, where odor identification occurs. The close anatomic ties between the olfactory system and the amygdala, hippocampus, and hypothalamus help to explain the intimate associations between odor perception and cognitive functions such as memory, motivation, arousal, autonomic activity, digestion, and sex. The sense of taste also employs chemoreceptors.

I-82. **The answer is D.** *(Chap. 29)* Taste information (Figure I-82) is sent to the brain via three cranial nerves (CNs): CN VII (the *facial nerve),* which involves the intermediate nerve with its branches, the greater petrosal and chorda tympani nerves; CN IX (the *glossopharyngeal nerve*); and CN X (the *vagus nerve*). CN VII innervates the anterior tongue and all of the soft palate; CN IX innervates the posterior tongue; and CN X innervates the laryngeal surface of the epiglottis, larynx, and proximal portion of the esophagus. The mandibular branch of CN V (V_3) conveys somatosensory information (e.g., touch, burning, cooling, irritation) to the brain. Although not technically a gustatory nerve, CN V shares primary nerve routes with many of the gustatory nerve fibers and adds temperature, texture, pungency, and spiciness to the taste experience. The chorda tympani nerve is famous for taking a recurrent course through the facial canal in the petrosal portion of the temporal bone, passing through the middle ear, and then exiting the skull via the petrotympanic

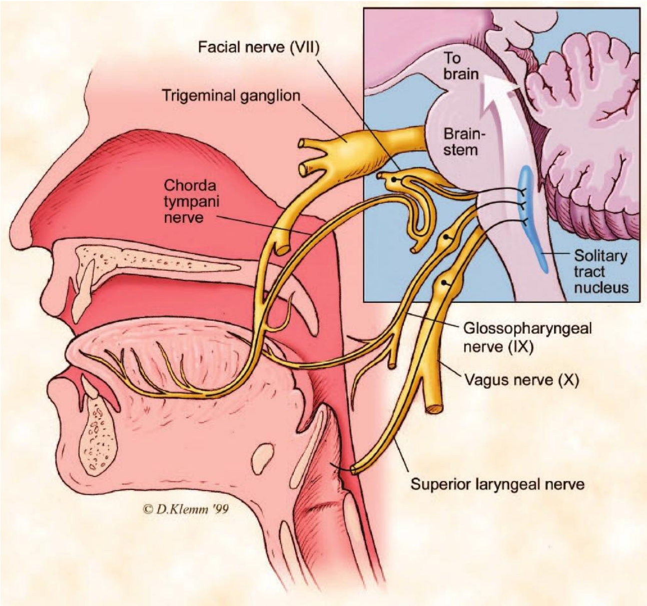


FIGURE I-82 Used with permission from David Klemm, Faculty and Curriculum Support (FACS), Georgetown University Medical Center.

fissure, where it joins the lingual nerve (a division of CN V) near the tongue. This nerve also carries parasympathetic fibers to the submandibular and sublingual glands, whereas the greater petrosal nerve supplies the palatine glands, influencing saliva production.

I-83. **The answer is C.** *(Chap. 29)* Presbyosmia (age-related olfactory deficits) and anosmia (olfactory deficit at any age) are relatively common. The ability to smell is influenced, in everyday life, by such factors as age, gender, general health, nutrition, smoking, and reproductive state. Women typically outperform men on tests of olfactory function and retain normal smell function to a later age than men do. Significant decrements in the ability to smell are present in over 50% of the population between 65 and 80 years of age and in 75% of those 80 years of age and older. Presbyosmia is much more than a nuisance and can confer real health risk. Such presbyosmia helps to explain why many elderly report that food has little flavor, a problem that can result in nutritional disturbances. This also helps to explain why a disproportionate number of elderly die in accidental gas poisonings. Although rare, patients with trauma-related anosmia can indeed recover olfactory function. Ten percent of posttraumatic anosmic patients will recover age-related normal function over time. This increases to nearly 25% of those with less than total loss. Olfactory impairment can be an early sign of Parkinson disease, often predating the clinical diagnosis by at least 4 years.

I-84. **The answer is C.** *(Chaps. 29 and 433)* Mr. McEvoy is suffering from Bell palsy, a dysfunction of CN VII. Bell palsy is one of the most common causes of CN VII injury that results in taste disturbance. The most common etiology of Bell palsy is likely a viral involvement (often varicella-zoster virus or herpes simplex virus) of the cranial nerve, and patients recover spontaneously or with steroid therapy. Clinicians should also consider more dire etiologies, such as Lyme disease or demyelinating diseases in the differential diagnosis.

I-85. **The answer is E.** *(Chap. 30)* Hearing loss is a common complaint, particularly in older individuals. In this age group, 33% of people have hearing loss to a degree that requires hearing aids. When evaluating hearing loss, the physician should attempt to determine whether the cause is conductive, sensorineural, or mixed. Sensorineural hearing loss results from injury of the cochlear apparatus or disruption of the neural pathways from the inner ear to the brain. The primary site of damage is the hair cells of the inner ear. Common causes of hair cell injury include prolonged exposure to loud noises, viral infections, ototoxic drugs, cochlear otosclerosis, Meniere disease, and aging. In contrast, conductive hearing loss results from impairment of the external ear and auditory canal to transmit and amplify sound through the middle ear to the cochlea. Causes of conductive hearing loss include cerumen impaction, perforations of the tympanic membrane, otosclerosis, cholesteatomas, large middle ear effusions, and tumors of the external auditory canal or middle ear among others. The initial physical examination can often differentiate between conductive and sensorineural hearing loss. Examination of the external auditory canal can identify cerumen or foreign body impaction. On otoscopic examination, it is more important to assess the topography of the tympanic membrane than look for the presence of a light reflex. Of particular attention is the area in the upper third of the tympanic membrane known as the pars flaccida. This area can develop chronic retraction pockets that are indicative of Eustachian tube dysfunction or a cholesteatoma, a benign tumor comprised of keratinized squamous epithelium. Bedside tests with a tuning fork also are useful for differentiating conductive from sensorineural hearing loss. In the Rinne test, air conduction is compared with bony conduction of sound. A tuning fork is placed over the mastoid process and then in front of the external ear. In conductive hearing loss, the intensity of sound is louder when placed on the bone, whereas in sensorineural hearing loss, the intensity is greatest at the external ear. In the Weber test, the tuning fork is placed in the midline of the head. In unilateral conductive hearing loss, the intensity of sound is loudest in the affected ear, whereas in unilateral sensorineural hearing loss, the intensity of sound is loudest in the unaffected ear. This patient reports left greater than right hearing loss that is suspected to be sensorineural in nature. Thus, the sound would be expected to be greatest in the right ear on the Weber test.

I-86. **The answer is C.** *(Chap. 30)* Once hearing loss is established, the next diagnostic test is pure tone audiometry that plots hearing threshold versus frequency. Pure tone audiometry establishes the severity, type, and laterality of hearing loss. In this gentleman, high-frequency hearing loss would be expected based on his complaints of inability to hear the alarm tone of his digital watch. Tympanometry measures the impedance of the middle ear to sound and is useful in diagnosis of middle ear effusions. Radiologic studies are indicated for suspected anatomic abnormalities. Axial and coronal CT of the temporal bone is ideal for determining the caliber of the external auditory canal, integrity of the ossicular chain, and presence of middle ear or mastoid disease; it can also detect inner ear malformations. CT is also ideal for the detection of bone erosion with chronic otitis media and cholesteatoma. An MRI is superior to a CT for imaging of retrocochlear pathology such as vestibular schwannoma, meningioma, other lesions of the cerebellopontine angle, demyelinating lesions of the brainstem, and brain tumors. Both CT and MRI are equally capable of identifying inner ear malformations and assessing cochlear patency for preoperative evaluation of patients for cochlear implantation. Schirmer test is a test for the evaluation of dry eyes to quantify adequate tear production.

I-87. **The answer is A.** *(Chap. 31)* Acute sinusitis is a common complication of upper respiratory tract infections and is defined as sinusitis lasting less than 4 weeks (Table I-87). Acute sinusitis typically presents with nasal drainage and congestion, facial pain or pressure, and headache that is worse with lying down or bending forward. Presence of purulent drainage does not differentiate bacterial from viral causes of sinusitis. The vast majority of cases of acute sinusitis are due to viral infection. However, when patients with acute sinusitis present to a medical professional, antibiotics are prescribed more than 85% of the time. Indeed, this should not be the preferred treatment as most cases improve without antibiotic therapy. Rather, the initial approach to a patient with acute sinusitis should be symptomatic treatment with nasal decongestants and nasal saline lavage. If a patient has a history of allergic rhinitis or chronic sinusitis, nasal glucocorticoids can be prescribed as well. Antibiotic therapy is recommended in adults for symptom duration greater than 10 days and for any patient with concerning severe symptoms (of any duration) such as unilateral or focal facial pain, swelling, or tooth pain. The initial antibiotic of choice for acute sinusitis is amoxicillin/clavulanate 500/125 mg. In patients with a penicillin allergy, doxycycline or antipneumococcal fluoroquinolone is the preferred agent. Ten percent of individuals do not

TABLE I-87 **Guidelines for the Diagnosis and Treatment of Acute Bacterial Sinusitis in Adults**

Diagnostic Criteria	Treatment Recommendations[a]
Moderate symptoms (e.g., nasal purulence/congestion or cough) for >10 d ***or*** Severe symptoms of any duration, including unilateral/focal facial swelling or tooth pain	*Initial therapy:* Amoxicillin/clavulanate, 500/125 mg PO tid or 875/125 mg PO bid[b] *Penicillin allergy:* Doxycycline, 100 mg PO bid; ***or*** An antipneumococcal fluoroquinolone (e.g., moxifloxacin, 400 mg/d PO daily)[c] *Exposure to antibiotics within 30 d or >30% prevalence of penicillin-resistant Streptococcus pneumoniae:* Amoxicillin/clavulanate (extended release), 2000/125 mg PO bid; ***or*** Doxycycline, 100 mg PO bid; ***or*** An antipneumococcal fluoroquinolone (e.g., moxifloxacin, 400 mg PO daily)[c] *Recent treatment failure:* Amoxicillin/clavulanate (extended release), 2000 mg PO bid; ***or*** An antipneumococcal fluoroquinolone (e.g., moxifloxacin, 400 mg PO daily)[c]

[a] The duration of therapy is 5–7 days if symptoms improve within the first few days of treatment but can be up to 7–10 days, with appropriate follow-up. Severe disease may warrant IV antibiotics and consideration of hospital admission.

[b] In areas where the prevalence of antibiotic resistance is low, amoxicillin can be considered as initial therapy in patients without recent antibiotic exposure.

[c] Fluoroquinolones carry a risk of tendinitis and neuropathy and should be used only if other options are not reasonable, with consideration of risks and benefits.

respond to initial antibiotic therapy. In this case, one can consider referral to otolaryngology for sinus aspiration and culture. Radiologic imaging of the sinuses is not recommended for evaluation of acute disease unless the sinusitis is nosocomially acquired because the procedures (CT or radiograph) do not differentiate between bacterial or viral causes.

I-88. **The answer is E.** *(Chap. 31)* This patient is presenting with *Ludwig* angina, which is a rapidly progressive, potentially fulminant form of cellulitis that involves the bilateral sublingual and submandibular spaces and that typically originates from an infected or recently extracted tooth, most commonly a lower second or third molar. Improved dental care has reduced the incidence of this disorder substantially. Infection in these areas leads to dysphagia, odynophagia, and "woody" edema in the sublingual region, forcing the tongue up and back with the potential for airway obstruction. Fever, dysarthria, and drooling also may occur, and patients may speak in a "hot potato" voice. Intubation or tracheostomy may be necessary to secure the airway, as asphyxiation is the most common cause of death. Patients should be admitted to the hospital and closely monitored during treatment with IV antibiotics directed against streptococci and oral anaerobes. Recommended agents include ampicillin/sulbactam, clindamycin, or high-dose penicillin plus metronidazole. Outpatient management is not adequate for treatment.

I-89. **The answer is A.** *(Chap. 31)* This patient is presenting with acute epiglottitis. In this lateral soft-tissue radiograph of the neck, the arrow indicates the enlarged edematous epiglottis (the "thumbprint sign"). *Acute epiglottitis* (supraglottitis) is an acute, rapidly progressive form of cellulitis of the epiglottis and adjacent structures that can result in complete—and potentially fatal—airway obstruction in both children and adults. Before the widespread use of *Haemophilus influenzae* type b (Hib) vaccine, this entity was much more common among children, with a peak incidence at ~3.5 years of age. In some countries, mass vaccination against Hib has reduced the annual incidence of acute epiglottitis in children by >90%; in contrast, the annual incidence in adults has changed little since the introduction of Hib vaccine. Lack of vaccination or vaccine failure has meant that many pediatric cases seen today are still due to Hib. In adults and (more recently) in children, a variety of other bacterial pathogens have been associated with epiglottitis; the most common is group A *Streptococcus*. Other pathogens, seen less frequently, include *Streptococcus pneumoniae*, *H. parainfluenzae*, and *Staphylococcus aureus* (including methicillin-resistant *S. aureus*). Viruses have not been established as causes of acute epiglottitis.

I-90. **The answer is A.** *(Chap. 31)* Although the patient likely has a middle ear infection, the CT shows an acute fluid collection in the left mastoid air cells consistent with acute mastoiditis. In typical acute mastoiditis, purulent exudate collects in the mastoid air cells, producing pressure that may result in erosion of the surrounding bone and formation of abscess-like cavities that are usually evident on CT. Patients typically present with pain, erythema, and swelling of the mastoid process along with displacement of the pinna, usually in conjunction with the typical signs and symptoms of acute middle ear infection. Rarely, patients can develop severe complications if the infection tracks under the periosteum of the temporal bone to cause a subperiosteal abscess, erodes through the mastoid tip to cause a deep neck abscess, or extends posteriorly to cause septic thrombosis of the lateral sinus. Purulent fluid should be cultured whenever possible to help guide antimicrobial therapy. Initial empirical therapy usually is directed against the typical organisms associated with acute otitis media, such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. Patients with more severe or prolonged courses of illness should be treated for infection with *Staphylococcus aureus* and gram-negative bacilli (including *Pseudomonas* spp.). Most patients can be treated conservatively with IV antibiotics; surgery (cortical mastoidectomy) is reserved for complicated cases and those in which conservative treatment has failed. The CT does not show a mass suggesting meningioma. In the absence of diabetes, poorly controlled hyperglycemia, and a destructive invasive inflammatory process, mucormycosis is not likely.

I-91. **The answer is B.** *(Chap. 31)* Approximately 5–15% of all cases of acute pharyngitis in adults are caused by *Streptococcus pyogenes*. Appropriate identification and treatment of *S. pyogenes* with antibiotic therapy is recommended to decrease the small risk of acute rheumatic fever. In addition, treatment with antibiotics within 48 hours of onset of symptoms decreases symptom duration and, importantly, decreases transmission of streptococcal pharyngitis. In adults, the recommended diagnostic procedure by the Centers for Disease Control and Prevention and the Infectious Diseases Society of America is a rapid antigen detection test for group A streptococci only. In children, however, the recommendation is to perform a throat culture for confirmation if the rapid screen is negative to limit the spread of disease and minimize potential complications. Throat culture generally is regarded as the most appropriate diagnostic method but cannot discriminate between colonization and infection. In addition, it takes 24–48 hours to get a result. Because most cases of pharyngitis at all ages are viral in origin, empiric antibiotic therapy is not recommended.

I-92. **The answer is D.** *(Chap. 32)* Saliva is essential to oral health. Its absence leads to dental caries, periodontal disease, and difficulties in wearing dental prostheses, masticating, and speaking. Its major components, water and mucin, serve as a cleansing solvent and lubricating fluid. In addition, saliva contains antimicrobial factors (e.g., lysozyme, lactoperoxidase, secretory IgA), epidermal growth factor, minerals, and buffering systems. The major salivary glands secrete intermittently in response to autonomic stimulation, which is high during a meal but low otherwise. Hundreds of minor glands in the lips and cheeks secrete mucus continuously throughout the day and night. Consequently, oral function becomes impaired when salivary function is reduced. The sensation of a dry mouth (*xerostomia*) is perceived when salivary flow is reduced by 50%. The most common etiology is medication, especially drugs with anticholinergic properties, but also alpha and beta blockers, calcium channel blockers, and diuretics. Other causes include Sjögren syndrome, chronic parotitis, salivary duct obstruction, diabetes mellitus, HIV/AIDS, and radiation therapy that includes the salivary glands in the field (e.g., for Hodgkin lymphoma and for head and neck cancer). Management involves the elimination or limitation of drying medications, preventive dental care, and supplementation with oral liquid or salivary substitutes. Sugarless mints or chewing gum may stimulate salivary secretion if dysfunction is mild. When sufficient exocrine tissue remains, pilocarpine or cevimeline have been shown to increase secretions. Commercial saliva substitutes or gels relieve dryness.

I-93. **The answer is E.** *(Chap. 32)* The clue to diagnosis in this patient is a painless mouth ulcer. The image shows oral leukoplakia. Ulceration is the most common oral mucosal lesion. Most acute ulcers are painful and self-limited. Recurrent aphthous ulcers and herpes simplex account for the majority. Persistent and deep aphthous ulcers can be idiopathic or can accompany HIV/AIDS. Aphthous lesions are often the presenting symptom in Behçet syndrome. Similar-appearing, though less painful, lesions may occur in reactive arthritis, and aphthous ulcers are occasionally present during phases of discoid or systemic lupus erythematosus. Aphthous-like ulcers are seen in Crohn disease, but, unlike the common aphthous variety, they may exhibit granulomatous inflammation on histologic examination. Recurrent aphthae are more prevalent in patients with celiac disease and have been reported to remit with elimination of gluten. Of major concern are chronic, relatively painless ulcers and mixed red/white patches (erythroplakia and leukoplakia) of >2 weeks in duration. Squamous cell carcinoma and premalignant dysplasia should be considered early and a diagnostic biopsy performed. High-risk sites include the lower lip, floor of the mouth, ventral and lateral tongue, and soft palate–tonsillar pillar complex. Significant risk factors for oral cancer in Western countries include sun exposure (lower lip), tobacco and alcohol use, and human papillomavirus infection. Syphilitic chancre may also present with a painless oral ulcer.

I-94. **The answer is D.** *(Chap. 33)* Dyspnea is defined as the subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. The experience derives from interactions among multiple physiologic, psychological, social, and environmental factors and may induce secondary physiologic and behavioral responses. Dyspnea, a symptom, can be perceived only by the person experiencing it and, therefore, must be self-reported. In contrast, signs of increased work of breathing, such as tachypnea, accessory muscle use, and intercostal retraction, can be measured and reported by clinicians. Up to one-half of inpatients and one-quarter of ambulatory patients experience dyspnea. Furthermore, it is increasingly appreciated that the degree of dyspnea may better predict outcomes in chronic obstructive pulmonary disease (COPD) than does the forced expiratory volume in 1 second (FEV_1), and formal measures of dyspnea have been incorporated into the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017 COPD severity assessment guidelines. Chronic dyspnea, which is defined as symptoms lasting longer than 1 month, can arise from a broad array of different underlying conditions, most commonly attributable to pulmonary or cardiac conditions that account for as many as 85% of the underlying causes of dyspnea. However, as many as one-third of patients may have multifactorial reasons underlying dyspnea (Figure I-94).

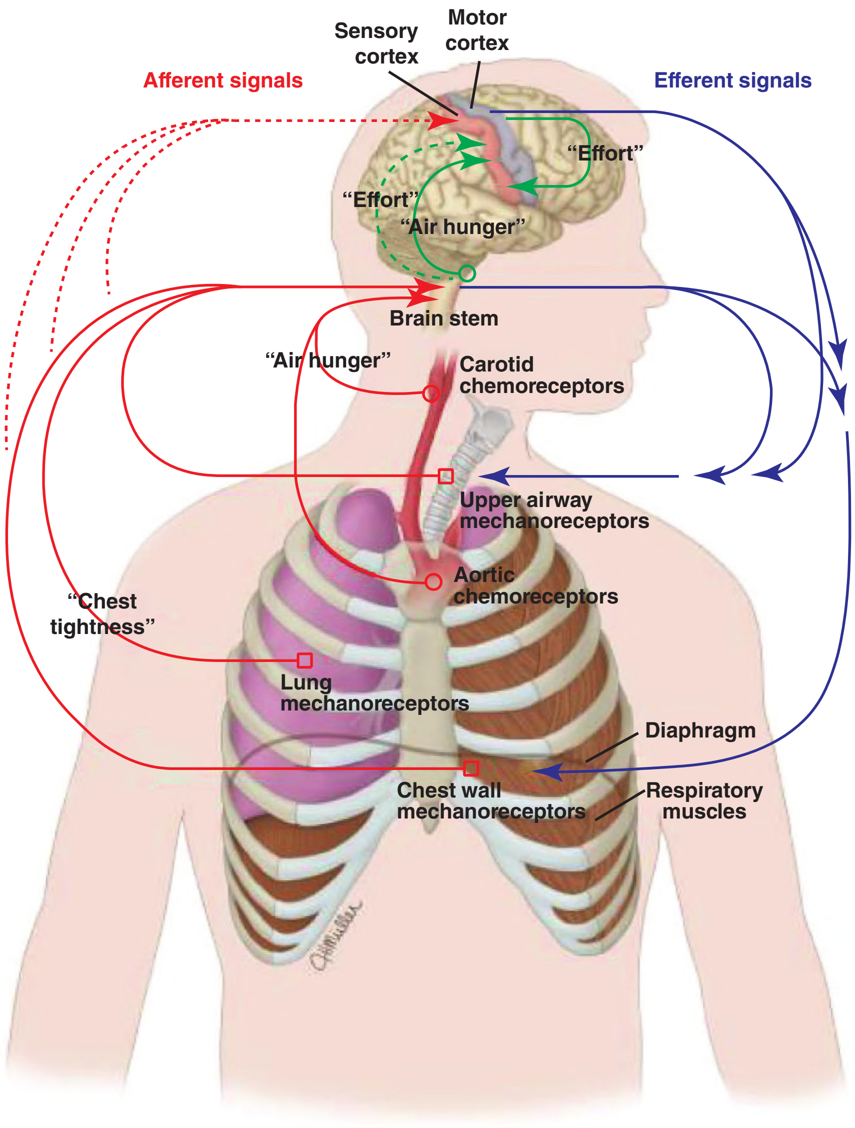


FIGURE I-94 Signaling pathways underlying dyspnea. Dyspnea arises from a range of sensory inputs, many of which lead to distinct descriptive phrases used by patients (shown in quotes in the figure). The sensation of respiratory effort likely arises from signals transmitted from the motor cortex to the sensory cortex (*green arrow*) when outgoing motor commands are sent to the ventilatory muscles (*efferent signals, blue arrow*). Motor output from the brainstem (*blue arrow*) may also be accompanied by signals transmitted to the sensory cortex and contribute to the sensation of effort (*dotted green arrow*). The sensation of air hunger probably derives from a combination of stimuli that increase the drive to breathe such as hypoxemia or hypercapnia (mediated by signals from chemoreceptors in the carotid body and aortic arch, indicated by afferent signals in red), acute hypercapnia or acidemia (mediated by signals from the peripheral and central chemoreceptors, indicated by afferent signals in red), airway and interstitial inflammation (mediated by pulmonary afferents, indicated by afferent signals in red), and pulmonary vascular receptors. Dyspnea arises in part from a perceived mismatch between the outgoing efferent messages to the ventilatory muscles and incoming afferent signals from the lungs and chest wall. Chest tightness, often associated with bronchospasm, is largely mediated by stimulation of vagal-irritant receptors. Afferent signals (*red arrows*) from airway, lung, and chest wall mechanoreceptors most likely pass through the brainstem before being transmitted to sensory cortex, although it is also possible that some afferent information bypasses the brainstem and goes directly to sensory cortex (*dotted arrow*). Red arrows and text, afferent signals; blue arrows and text, efferent signals; green arrows, signals within the central nervous system; dotted lines, hypothetical pathways; hollow red circles, chemoreceptors; hollow red squares, mechanoreceptors. (Reproduced with permission from Schwartzstein RM: Approach to the patient with dyspnea. In: UpToDate, Post TW [ed], UpToDate, Waltham, MA. [January 26, 2021] Copyright © 2021 UpToDate, Inc.)

Afferent signals trigger the central nervous system (brainstem and/or cortex) and include primarily (1) peripheral chemoreceptors in the carotid body and aortic arch and central chemoreceptors in the medulla that are activated by hypoxemia, hypercapnia, or acidemia, and might produce a sense of "air hunger," and (2) mechanoreceptors in the upper airways, lungs (including stretch receptors, irritant receptors, and J receptors), and chest wall (including muscle spindles as stretch receptors and tendon organs that monitor force generation) that are activated in the setting of an increased work load from a disease state producing an increase in airway resistance that may be associated with symptoms of chest tightness (e.g., asthma or COPD) or decreased lung or chest wall compliance (e.g., pulmonary fibrosis).

I-95. **The answer is C.** *(Chap. 34)* Beta blockers do not commonly cause cough. Angiotensin-converting enzyme (ACE) inhibitors are the medication most often associated with cough. ACE inhibitor–induced cough occurs in 5–30% of patients taking these agents and is not dose dependent. ACE metabolizes bradykinin and other tachykinins, such as substance P. The mechanism of ACE inhibitor–associated cough may involve sensitization of sensory nerve endings due to accumulation of bradykinin. Any patient with chronic unexplained cough who is taking an ACE inhibitor should have a trial period off the medication, regardless of the timing of the onset of cough relative to the initiation of ACE inhibitor therapy. Angiotensin receptor blockers (ARBs) do not typically cause cough and may be substituted in a patient with suspected ACE-inhibitor cough. The selective bulbous enlargement of the distal segments of the fingers and toes due to proliferation of connective tissue, particularly on the dorsal surface, is termed *clubbing*; there is also increased sponginess of the soft tissue at the base of the clubbed nail. Clubbing may be hereditary, idiopathic, or acquired and associated with a variety of disorders, including cyanotic congenital heart disease, infective endocarditis, and a variety of pulmonary conditions (among them primary and metastatic lung cancer, bronchiectasis, asbestosis, sarcoidosis, lung abscess, cystic fibrosis, tuberculosis, and mesothelioma), as well as with some gastrointestinal diseases (including inflammatory bowel disease and hepatic cirrhosis). In addition to examination of the nasal passageways for rhinitis or polyps, it is also important to examine the auditory canals and tympanic membranes because irritation of these may stimulate the Arnold nerve and cause cough. It is thought that reflux of gastric contents into the lower esophagus may trigger cough via reflex pathways initiated in the esophageal mucosa. Reflux to the level of the pharynx (laryngopharyngeal reflux), with consequent aspiration of gastric contents, causes a chemical bronchitis and possibly pneumonitis that can elicit cough for days afterward, but it is a rare finding among persons with chronic cough. Retrosternal burning after meals or on recumbency, frequent eructation, hoarseness, and throat pain may be indicative of gastroesophageal reflux. Nevertheless, reflux may also elicit minimal or no symptoms. In a long-time cigarette smoker, an early-morning, productive cough suggests chronic bronchitis.

I-96. **The answer is A.** *(Chap. 34)* Although common in everyday life, the cough reflex is really quite intricate. Spontaneous cough is triggered by stimulation of sensory nerve endings that are thought to be primarily rapidly adapting receptors and C fibers. Both chemical (e.g., capsaicin) and mechanical (e.g., particulates in air pollution) stimuli may initiate the cough reflex. A cationic ion channel—the transient receptor potential vanilloid 1 (TRPV1)—found on rapidly adapting receptors and C fibers is the receptor for capsaicin, and its expression is increased in patients with chronic cough. Afferent nerve endings richly innervate the pharynx, larynx, and airways to the level of the terminal bronchioles and extend into the lung parenchyma. They may also be located in the external auditory meatus (the auricular branch of the vagus nerve, or Arnold nerve) and in the esophagus. Sensory signals travel via the vagus and superior laryngeal nerves to a region of the brainstem in the nucleus tractus solitarius vaguely identified as the "cough center." The vocal cords adduct, leading to transient upper airway occlusion. Expiratory muscles contract, generating positive intrathoracic pressures as high as 300 mmHg. With sudden release of the laryngeal contraction, rapid expiratory flows are generated, exceeding the normal "envelope" of maximal expiratory flow seen on the flow-volume curve (Figure I-96). Bronchial smooth-muscle contraction together with dynamic compression of airways narrows airway lumens and maximizes the velocity of exhalation. The kinetic energy

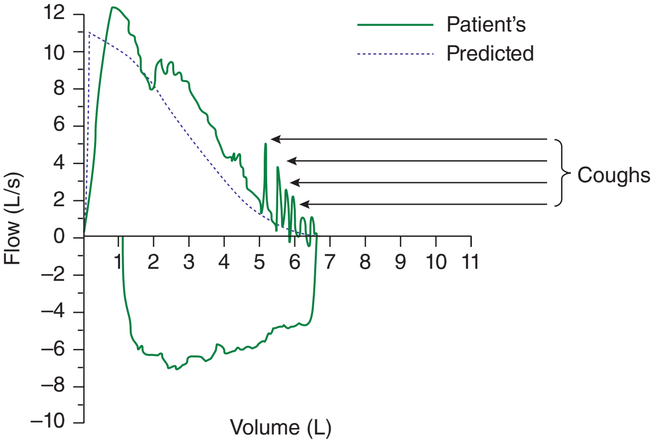


FIGURE I-96

available to dislodge mucus from the inside of airway walls is directly proportional to the square of the velocity of expiratory airflow. A deep breath preceding a cough optimizes the function of the expiratory muscles; a series of repetitive coughs at successively lower lung volumes sweeps the point of maximal expiratory velocity progressively further into the lung periphery.

I-97. **The answer is B.** *(Chap. 35)* Patients with bronchiectasis (a permanent dilation of the airways with loss of mucosal integrity) are particularly prone to hemoptysis due to chronic inflammation and anatomic abnormalities that bring the bronchial arteries closer to the mucosal surface. One common presentation of patients with advanced cystic fibrosis—the prototypical bronchiectatic lung disease—is hemoptysis, which can be life-threatening. Significant hemoptysis can result from the proximity of the bronchial artery and vein to the airway, with these vessels and the bronchus running together in what is often referred to as the bronchovascular bundle. In the smaller airways, these blood vessels are close to the airspace, and lesser degrees of inflammation or injury can therefore result in their rupture into the airways. Although alveolar hemorrhage arises from capillaries that are part of the low-pressure pulmonary circulation, bronchial bleeding generally originates from bronchial arteries, which are under systemic pressure and thus are predisposed to larger volume bleeding.

I-98. **The answer is D.** *(Chap. 35)* Mr. Boyle is suffering from a large-volume life-threatening hemoptysis. As noted in the prior question, in this patient with cystic fibrosis and bronchiectasis, the culprit vessel is likely a bronchial artery. After initial stabilization, which almost always requires establishment of a patent airway with endotracheal intubation and mechanical ventilation and volume resuscitation, the goals are to isolate the bleeding to one lung and not to allow the preserved airspaces in the other lung to be filled with blood so that gas exchange is further impaired. Patients should be placed with the bleeding lung in a dependent position (i.e., bleeding side down; in this case the right side), and if possible, dual lumen endotracheal tubes or an airway blocker should be placed in the proximal airway of the bleeding lung.

I-99. **The answer is C.** *(Chap. 36)* In the evaluation of cyanosis, the first step is to differentiate central from peripheral cyanosis. In central cyanosis, because the etiology is either reduced oxygen saturation or abnormal hemoglobin, the physical findings include bluish discoloration of both mucous membranes and skin. In contrast, peripheral cyanosis is associated with normal oxygen saturation but slowing of blood flow and an increased fraction of oxygen extraction from blood; subsequently, the physical findings are present only in the skin and extremities. Mucous membranes are spared. In this case, all of the options are causes of peripheral cyanosis, except for hereditary hemorrhagic telangiectasia. In this disorder, patients develop pulmonary arteriovenous fistulae that lead to right-to-left shunting and central cyanosis. Pulmonary arteriovenous fistula or arteriovenous malformations may be congenital or acquired, solitary or multiple, microscopic or massive.

The severity of cyanosis produced by these fistulae depends on their size and number. Probably the most common cause of peripheral cyanosis is the normal vasoconstriction resulting from exposure to cold air or water. When cardiac output is reduced, cutaneous vasoconstriction occurs as a compensatory mechanism so that blood is diverted from the skin to more vital areas such as the central nervous system and heart, and cyanosis of the extremities may result even though the arterial blood is normally saturated. Arterial obstruction to an extremity, as with an embolus, or arteriolar constriction, as in cold-induced vasospasm (Raynaud phenomenon), generally results in pallor and coldness, and there may be associated cyanosis. Venous obstruction, as in thrombophlebitis or deep venous thrombosis, dilates the subpapillary venous plexuses and intensifying cyanosis.

I-100. **The answer is D.** *(Chap. 36)* Acute hypoxia stimulates the chemoreceptor reflex arc to induce venoconstriction and systemic arterial vasodilation. These acute changes are accompanied by transiently increased myocardial contractility, which is followed by depressed myocardial contractility with prolonged hypoxia. In pulmonary vascular smooth-muscle cells, inhibition of K^+ channels causes depolarization which, in turn, activates voltage-gated Ca^{2+} channels raising the cytosolic [Ca^{2+}] and causing smooth-muscle cell contraction. Hypoxia-induced pulmonary arterial constriction shunts blood away from poorly ventilated portions toward better ventilated portions of the lung; however, it also increases pulmonary vascular resistance and right ventricular afterload. Chronic hypoxia leads to multiple adaptive changes in human physiology. It is believed that upregulation of hypoxia-inducible factor 1 (HIF-1) leads to increased expression of vascular endothelial growth factor, which augments angiogenesis, and erythropoietin, which enhances erythrocyte production. The seminal work on HIF-1 was awarded the Nobel Prize in Medicine in 2019.

I-101. **The answer is A.** *(Chap. 36)* Options B–E all are examples of hypoxia due to respiratory failure and characterized by elevated $PaCO_2$. In instances of elevated partial pressure of carbon dioxide, the oxygen–hemoglobin dissociation curve shifts to the right. Thus, for any given arterial partial pressure of oxygen, the arterial hemoglobin will be lower. In normal physiologic circumstances, this is advantageous as hemoglobin is more likely to release oxygen (become less saturated) in areas where CO_2 is most prevalent (the target tissues of perfusion). As opposed to the other choices, the woman in option A will actually be hyperventilating and thus have a lower $PaCO_2$. This will shift the oxygen–hemoglobin dissociation curve to the left from baseline (known as the Bohr effect). Thus, for the given PaO_2 of 60 mmHg, she will have a higher arterial hemoglobin oxygen saturation.

I-102. **The answer is C.** *(Chap. 36)* Cyanosis is most importantly determined by the absolute, not relative, quantity of reduced hemoglobin (deoxygenated hemoglobin) or hemoglobin derivative (methemoglobin or sulfhemoglobin) in the capillary blood. In general, cyanosis becomes apparent when the concentration of reduced hemoglobin exceeds 4 g/dL. Thus, if two patients have identical relative concentrations of reduced hemoglobin (e.g., these patients with a hemoglobin saturation of 80% have 20% deoxygenated, or reduced, hemoglobin in their arterial blood), the patient with the highest absolute hemoglobin concentration will appear most cyanotic. As an example, we can consider the arterial blood of the patients in options A and C (although it is capillary blood that determines the appearance of cyanosis). The patient in option A has a hemoglobin concentration of 8 g/dL. If 20% of that is reduced, he will have an absolute amount of reduced hemoglobin of 1.6 g/dL; he may not appear cyanotic at all. However, the patient in option C, with the same relative 20% of his hemoglobin reduced, will have an absolute amount of reduced hemoglobin of 4 g/dL and will readily appear cyanotic. Thus, in a patient with severe anemia, the relative quantity of reduced hemoglobin in the venous blood may be very large when considered in relation to the total quantity of hemoglobin in the blood. However, since the concentration of the latter is markedly reduced, the absolute quantity of reduced hemoglobin may still be low; therefore, patients with severe anemia and even marked arterial desaturation may not display cyanosis. Conversely, the higher the total hemoglobin content, the greater is the tendency toward cyanosis; thus, patients with marked polycythemia tend to be cyanotic at higher levels of SaO_2 than patients with normal hematocrit values.

I-103. **The answer is B.** *(Chaps. 38 and 260)* Mitral valve prolapse (MVP), also variously termed the *systolic click-murmur syndrome, Barlow syndrome, floppy-valve syndrome, and billowing mitral leaflet syndrome*, is a relatively common but highly variable clinical syndrome resulting from diverse pathologic mechanisms of the mitral valve apparatus. MVP is the most common abnormality leading to primary mitral regurgitation (MR). A midsystolic nonejection sound (C) occurs in MVP and is followed by a late systolic murmur that crescendos to the second heart sound (S_2). A late systolic murmur that is best heard at the left ventricular apex is usually due to MVP. Standing decreases venous return, the heart becomes smaller, C moves closer to the first heart sound (S_1), and the mitral regurgitant murmur has an earlier onset. With prompt squatting, venous return and afterload increase; the heart becomes larger; C moves toward S_2; and the duration of the murmur shortens (Figure I-103).

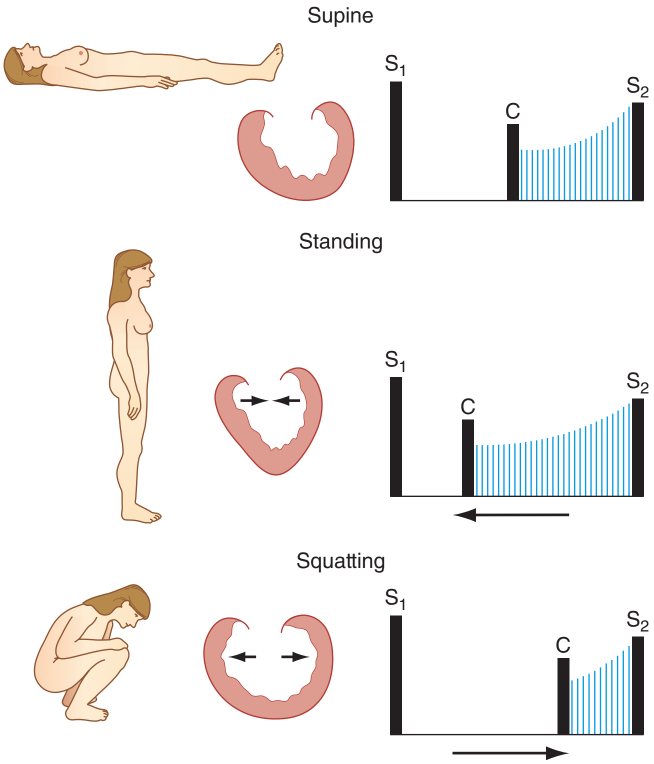


FIGURE I-103 Reprinted with permission *Examination of the Heart Part IV: Auscultation of the Heart* ©1990, American Heart Association, Inc.

I-104. **The answer is D.** *(Chap. 38)* Acute, severe mitral regurgitation (MR) into a normal-sized, relatively noncompliant left atrium results in an early decrescendo systolic murmur best heard at or just medial to the apical impulse (Figure I-104). This murmur is often very soft, and indeed, approximately 50% of cases of acute severe MR have no murmur at all. These characteristics reflect the progressive attenuation of the pressure gradient between the left ventricle and the left atrium during systole because of the rapid rise in left atrial pressure caused by the sudden volume load into an unprepared, noncompliant chamber and contrast sharply with the auscultatory features of chronic MR. Clinical settings in which acute, severe MR occur include (1) papillary muscle rupture complicating acute myocardial infarction, (2) rupture of chordae tendineae in the setting of myxomatous mitral valve disease, (3) infective endocarditis (which is likely the case for Mr. Carpentier), and (4) blunt chest wall trauma. The murmur is to be distinguished from that associated with post–myocardial infarction ventricular septal rupture, which is accompanied by a systolic thrill at the left sternal border in nearly all patients and is holosystolic in duration. The holosystolic murmur of chronic MR is best heard at the left ventricular apex and radiates to the axilla; it is usually high pitched and plateaued in configuration because of the wide difference between left ventricular and left atrial pressure throughout systole. In contrast to acute MR, left atrial compliance is

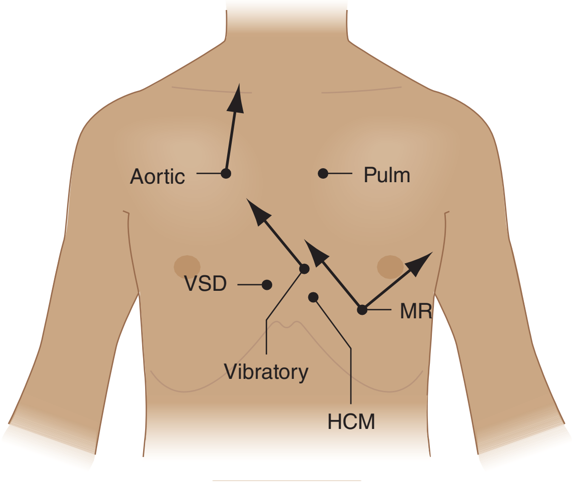


FIGURE I-104 *Abbreviations:* HCM, hypertrophic cardiomyopathy; MR, mitral regurgitation; Pulm, pulmonary; VSD, ventricular septal defect. (Reproduced with permission from Barlow JB: *Perspectives on the Mitral Valve*. Philadelphia: FA Davis, 1987.)

normal or even increased in chronic MR. As a result, there is only a small increase in left atrial pressure for any increase in regurgitant volume.

I-105. **The answer is E.** *(Chap. 38)* The obstructive form of hypertrophic cardiomyopathy (HCM) is associated with a midsystolic murmur that is usually loudest along the left sternal border or between the left lower sternal border and the apex. The murmur is produced by both dynamic left ventricular outflow tract obstruction and mitral regurgitation (MR); thus, its configuration is a hybrid between ejection and regurgitant phenomena. The intensity of the murmur may vary from beat to beat and after provocative maneuvers but usually does not exceed grade 3. The murmur classically will increase in intensity with maneuvers that result in increasing degrees of outflow tract obstruction, such as a reduction in preload or afterload (Valsalva, standing, vasodilators) or with an augmentation of contractility (inotropic stimulation such as milrinone). However, augmentation of contractility will also increase the intensity of the murmur of aortic stenosis, thus, it is not useful for differentiation. Augmentation of afterload (handgrip) is associated with diminished murmur intensity in both aortic stenosis (AS) and obstructive HCM. Maneuvers that increase preload (squatting, passive leg raising, volume administration) or afterload (squatting, vasopressors) or agents that reduce contractility (β-adrenoceptor blockers) decrease the intensity of the murmur of HCM. In contrast to AS, the carotid upstroke is rapid and of normal volume. Rarely, it is bisferiens or bifid in contour due to midsystolic closure of the aortic valve.

I-106. **The answer is D.** *(Chap. 38)* Chronic, severe atrial regurgitation (AR) may produce a lower-pitched mid to late, grade 1 or 2 diastolic murmur at the apex (Austin Flint murmur), which is thought to reflect turbulence at the mitral inflow area from the admixture of regurgitant (aortic) and forward (mitral) blood. This lower-pitched, apical diastolic murmur can be distinguished from that due to mitral stenosis (MS) by the absence of an opening snap and the response of the murmur to a vasodilator challenge. Lowering afterload with an agent such as amyl nitrite will decrease the duration and magnitude of the aortic–left ventricular diastolic pressure gradient, and thus, the Austin Flint murmur of severe AR will become shorter and softer. Increasing afterload (handgrip or phenylephrine) will have the opposite effect as the regurgitant volume through the incompetent aortic valve increases. The intensity of the diastolic murmur of MS may either remain constant or increase with afterload reduction (amyl nitrate or a calcium channel blocker such as nifedipine) because of the reflex increase in cardiac output and mitral valve flow.

I-107. **The answer is D.** *(Chap. 38)* Rheumatic fever is the most common cause of mitral stenosis (MS). In younger patients with pliable valves, S_1 is loud and the murmur begins after an opening snap, which is a high-pitched sound that occurs shortly after S_2. The interval between the pulmonic component of the second heart sound (P_2) and the opening snap is inversely related to the magnitude of the left atrial–left ventricular pressure gradient. The murmur of MS is low pitched and thus is best heard with the bell of the stethoscope. It is loudest at the left ventricular apex and often is appreciated only when the patient is turned in the left lateral decubitus position. It is usually of grade 1 or 2 intensity but may be absent when the cardiac output is severely reduced despite significant obstruction. The intensity of the murmur increases during maneuvers that increase cardiac output and mitral valve flow, such as exercise. The duration of the murmur reflects the length of time over which left atrial pressure exceeds left ventricular diastolic pressure. An increase in the intensity of the murmur just before S_1, a phenomenon known as presystolic accentuation, occurs in patients in sinus rhythm and is due to a late increase in transmitral flow with atrial contraction. Presystolic accentuation does not occur in patients with atrial fibrillation, as is the case with Mrs. Edwards, because of the lack of effective atrial contraction.

I-108. **The answer is A.** *(Chap. 39)* Palpitations are brought about by cardiac (43%), psychiatric (31%), miscellaneous (10%), and unknown (16%) causes, according to one large series. It is important to note that most arrhythmias are not associated with palpitations. Among the cardiovascular causes are premature atrial and ventricular contractions, supraventricular and ventricular arrhythmias, mitral valve prolapse (with or without associated arrhythmias), aortic insufficiency, atrial myxoma, myocarditis, and pulmonary embolism. Intermittent palpitations are commonly caused by premature atrial or ventricular contractions: the post-extrasystolic beat is sensed by the patient because of the increase in ventricular end-diastolic dimension following the pause in the cardiac cycle and the increased strength of contraction (post-extrasystolic potentiation) of that beat. A resting electrocardiogram can be used to document the arrhythmia. If exertion is known to induce the arrhythmia and accompanying palpitations, exercise electrocardiography can be used to make the diagnosis. If the arrhythmia is sufficiently infrequent, other methods must be used, including continuous electrocardiographic (Holter) monitoring; telephonic monitoring, through which the patient can transmit an electrocardiographic tracing during a sensed episode; loop recordings (external or implantable), which can capture the electrocardiographic event for later review; and mobile cardiac outpatient telemetry. Data suggest that Holter monitoring is of limited clinical utility, while the implantable loop recorder and mobile cardiac outpatient telemetry are safe and possibly more cost-effective in the assessment of patients with (infrequent) recurrent, unexplained palpitations. The suggestion of swimming would be potentially very dangerous as Mr. Garibolldy runs the risk of passing out while in the water.

I-109. **The answer is D.** *(Chap. 40)* He likely has aspiration pneumonia based on his clinical presentation, radiographs, and description of his swallowing. Oral-phase dysphagia is associated with poor bolus formation and control so that food has prolonged retention within the oral cavity and may seep out of the mouth. Drooling and difficulty in initiating swallowing are other characteristic signs. If oral or pharyngeal dysphagia is suspected, as in this case, a fluoroscopic swallow study, usually done by a swallow therapist, is the procedure of choice. Otolaryngoscopy and neurologic evaluation also can be important, depending on the circumstances. For suspected esophageal dysphagia, upper endoscopy is the single most useful test. Endoscopy allows better visualization of mucosal lesions than does barium radiography and allows one to obtain mucosal biopsies. Endoscopic or histologic abnormalities are evident in the leading causes of esophageal dysphagia: Schatzki ring, gastroesophageal reflux disease, and eosinophilic esophagitis. Furthermore, therapeutic intervention with esophageal dilation can be done as part of the procedure if it is deemed necessary. A CT of the chest would be helpful if a mass lesion is expected and contributing to esophageal pathology. In this case with oropharyngeal dysphagia, CT of the neck would be more appropriate. Barium radiography can provide useful adjunctive information in cases of subtle or complex esophageal strictures, prior esophageal surgery, esophageal diverticula, or paraesophageal herniation.

I-110. **The answer is B.** *(Chap. 43)* Clinically important weight loss is defined as the loss of 10 pounds (4.5 kg) or >5% of one's body weight over a period of 6–12 months (Table I-110).

TABLE I-110 Assessment and Testing for Involuntary Weight Loss

Indications	Laboratory
5% weight loss in 30 d	Complete blood count
10% weight loss in 180 d	Comprehensive electrolyte and metabolic panel, including liver and renal function tests
Body mass index <21	Thyroid function tests
25% of food left uneaten after 7 d	Erythrocyte sedimentation rate
Change in fit of clothing	C-reactive protein
Change in appetite, smell, or taste	Ferritin
Abdominal pain, nausea, vomiting, diarrhea, constipation, dysphagia	HIV testing, if indicated
Assessment	Radiology
Complete physical examination, including dental evaluation	Chest x-ray Abdominal ultrasound
Medication review	
Recommended cancer screening	
Mini-Mental State Examination[a]	
Mini-Nutritional Assessment[a]	
Nutrition Screening Initiative[a]	
Simplified Nutritional Assessment Questionnaire[a]	
Observation of eating[a]	
Activities of daily living[a]	
Instrumental activities of daily living[a]	

[a] May be more specific to assess weight loss in the elderly.

Unintentional weight loss is encountered in up to 8% of all adult outpatients and 27% of frail persons aged ≥65 years. There is no identifiable cause in up to one-quarter of patients despite extensive investigation. Among healthy aging people, total body weight peaks in the sixth decade of life and generally remains stable until the ninth decade, after which it gradually falls. Weight loss in older persons is associated with a variety of deleterious effects, including falls and fractures, pressure ulcers, impaired immune function, and decreased functional status. Not surprisingly, significant weight loss is associated with increased mortality, which can range from 9% to as high as 38% within 1–2.5 years in the absence of clinical awareness and attention. Initial assessment includes a comprehensive history and physical, a complete blood count, tests of liver enzyme levels, C-reactive protein, erythrocyte sedimentation rate, renal function studies, thyroid function tests, chest radiography, and an abdominal ultrasound. Age, sex, and risk factor–specific cancer screening tests, such as mammography and colonoscopy, should be performed. Patients at risk should have HIV testing. All elderly patients with weight loss should undergo screening for dementia and depression by using instruments such as the Mini-Mental State Examination and the Geriatric Depression Scale, respectively. Almost all patients with a malignancy and >90% of those with other organic diseases have at least one laboratory abnormality.

I-111. **The answer is C.** *(Chap. 44)* Recent meta-analysis of randomized trials document that high-dose intermittent proton pump inhibitors (PPIs) are noninferior to constant-infusion PPI therapy and thus may be substituted in this population. Patients with lower risk findings (flat pigmented spot or clean base) do not require endoscopic therapy and receive standard doses of oral PPI. Prevention of recurrent bleeding focuses on the three main factors in ulcer pathogenesis: *Helicobacter pylori*, nonsteroidal anti-inflammatory drugs (NSAIDs), and acid. Eradication of *H. pylori* in patients with bleeding ulcers decreases rebleeding rates to <5%. If NSAIDs must be given, a cyclooxygenase (COX)-2-selective NSAID plus a PPI is recommended, based on results of a randomized trial. Patients with established cardiovascular disease who develop bleeding ulcers while taking low-dose aspirin for secondary prevention should restart aspirin as soon as possible after their bleeding episode (1–7 days). A randomized trial showed that failure to restart aspirin was associated with no significant difference in rebleeding (5% vs 10%) at 30 days but a significant increase in mortality (9% vs 1%) compared with immediate reinstitution of aspirin. Patients with bleeding ulcers unrelated to *H. pylori* or NSAIDs should remain on PPI therapy indefinitely given a 42% incidence of rebleeding at 7 years without protective therapy.

I-112. **The answer is C.** *(Chap. 45)* The differential diagnosis for yellowing of the skin is limited. In addition to jaundice, it includes carotenoderma, the use of the drug quinacrine, and excessive exposure to phenols. Carotenoderma is the yellow color imparted to the skin of healthy individuals who ingest excessive amounts of vegetables and fruits that contain carotene, such as carrots, leafy vegetables, squash, peaches, and oranges. In jaundice the yellow coloration of the skin is uniformly distributed over the body, whereas in carotenoderma the pigment is concentrated on the palms, soles, forehead, and nasolabial folds. Carotenoderma can be distinguished from jaundice by the sparing of the sclerae. Quinacrine causes a yellow discoloration of the skin in 4–37% of patients treated with it. Another sensitive indicator of increased serum bilirubin is darkening of the urine, which is due to the renal excretion of conjugated bilirubin. Patients often describe their urine as tea- or cola-colored. Bilirubinuria indicates an elevation of the direct serum bilirubin fraction and, therefore, the presence of liver or biliary disease.

I-113. **The answer is D.** *(Chap. 46)* The most telling laboratory value to calculate when assessing the etiology of ascites is the serum-ascites albumin gradient (SAAG). The SAAG is useful for distinguishing ascites caused by portal hypertension from non–portal hypertensive ascites. The SAAG reflects the pressure within the hepatic sinusoids and correlates with the hepatic venous pressure gradient. It is calculated by subtracting the ascitic albumin concentration from the serum albumin level and does not change with diuresis. A SAAG ≥1.1 g/dL reflects the presence of portal hypertension and indicates that the ascites is due to increased pressure in the hepatic sinusoids, as in cirrhosis. According to Starling's law, a high SAAG reflects the oncotic pressure that counterbalances the portal pressure. Possible causes include cirrhosis, cardiac ascites, hepatic vein thrombosis (chronic Budd-Chiari syndrome), sinusoidal obstruction syndrome (veno-occlusive disease), or massive liver metastases. A SAAG <1.1 g/dL indicates that the ascites is not related to portal hypertension, as in tuberculous peritonitis, peritoneal carcinomatosis, or pancreatic ascites. In this patient, the SAAG is 0.6 and therefore more likely to be peritoneal carcinomatosis rather than the other choices listed, which all produce a high SAAG. The ascitic protein is most helpful in distinguishing the high SAAG causes of ascites.

I-114. **The answer is E.** *(Chap. 46) Aerophagia*, the swallowing of air, can result in increased amounts of oxygen and nitrogen in the small intestine and lead to abdominal swelling. Aerophagia typically results from gulping food, chewing gum, smoking, or as a response to anxiety, which can lead to repetitive belching. Nitrogen and oxygen are consumed (swallowed), whereas carbon dioxide, hydrogen, and methane are produced intraluminally by bacterial fermentation. Weight gain with an increase in abdominal fat can result in an increase in abdominal girth and can be perceived as abdominal swelling. Abdominal fat may be caused by an imbalance between caloric intake and energy expenditure associated with a poor diet and sedentary lifestyle, but it has no association with gum chewing and is less likely a contributor.

I-115. **The answer is E.** *(Chap. 46)* Based on the high serum-ascites albumin gradient (SAAG) and low ascitic protein, he likely has cirrhosis (Figure I-115). The initial treatment for cirrhotic ascites is restriction of sodium intake to 2 g/d. When sodium restriction alone is inadequate to control ascites, oral diuretics—typically the combination of spironolactone and furosemide—are used. Spironolactone is an aldosterone antagonist that inhibits sodium reabsorption in the distal convoluted tubule of the kidney. Use of spironolactone may be limited by hyponatremia, hyperkalemia, and painful gynecomastia. Malignant ascites does not respond to sodium restriction or diuretics.

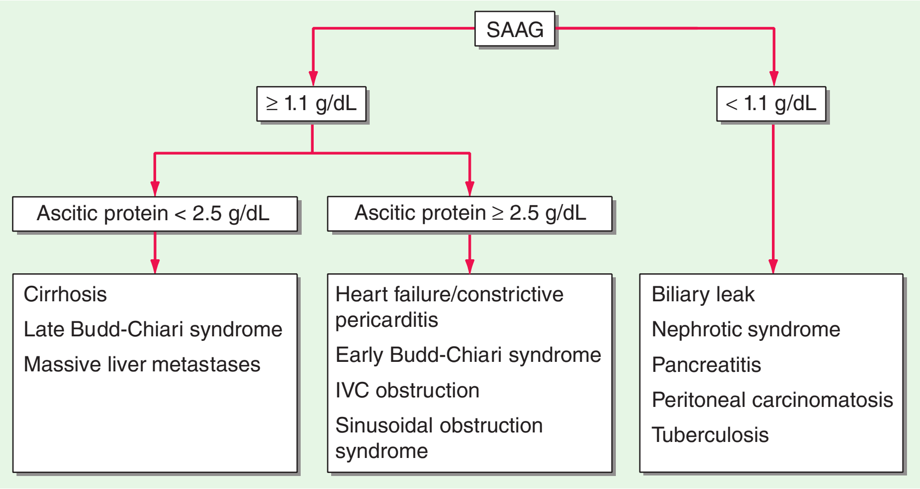

SAAG
≥ 1.1 g/dL
< 1.1 g/dL
Ascitic protein < 2.5 g/dL
Ascitic protein ≥ 2.5 g/dL
Cirrhosis
Late Budd-Chiari syndrome
Massive liver metastases
Heart failure/constrictive pericarditis
Early Budd-Chiari syndrome
IVC obstruction
Sinusoidal obstruction syndrome
Biliary leak
Nephrotic syndrome
Pancreatitis
Peritoneal carcinomatosis
Tuberculosis

FIGURE I-115 *Abbreviations:* IVC, inferior vena cava; SAAG, serum-ascites albumin gradient.

I-116. The answer is E. *(Chap. 46)* This patient presents with abdominal swelling due to ascites (one of the 6 "Fs" that represent the causes of abdominal swelling [fluid, fetus, fat, feces, flatus, fatal mass]) as is evidenced by the fluid wave and dullness to percussion on physical examination. A careful examination can often determine the underlying cause of ascites, particularly if it is due to elevated portal pressures. In this case, the patient has evidence of elevated pressure in the jugular veins (Kussmaul sign, where the jugular venous pulse fails to decrease with inspiration) and right ventricle (right ventricular heave and loud P_2 accompanied by the murmur of tricuspid regurgitation). These elevated right-sided cardiac pressures will back up into the hepatic veins. By necessity, the pressure in the portal vein must also elevate (as measured by the wedged hepatic vein pressure) to keep blood flowing forward.

I-117. The answer is C. *(Chap. 48)* Hematuria is defined as two to five red blood cells (RBCs) per high-power field (HPF) and can be detected by dipstick. A false-positive dipstick for hematuria (where no RBCs are seen on urine microscopy) may occur when myoglobinuria is present, often in the setting of rhabdomyolysis. This could be related to his statin. Common causes of isolated hematuria include stones, neoplasms, tuberculosis, trauma, and prostatitis. Hematuria with pyuria and bacteriuria is typical of infection and should be treated with antibiotics after appropriate cultures. Hypercalciuria and hyperuricosuria are also risk factors for unexplained isolated hematuria in both children and adults; however this patient does not have hematuria.

I-118. The answer is D. *(Chap. 48)* Acute renal failure can result from processes that affect renal blood flow (prerenal azotemia), intrinsic renal diseases (affecting small vessels, glomeruli, or tubules), or postrenal processes (obstruction of urine flow in ureters, bladder, or urethra). Differentiating between the processes narrows the differential diagnosis significantly. In this patient, the lack of hydronephrosis rules out obstructive uropathy, and the bland urinalysis and lack of urinary casts make glomerulonephritis, interstitial nephritis, or tubular necrosis unlikely. Control of vascular tone of the afferent glomerular arterioles is via prostaglandins. Prostaglandin antagonism with nonsteroidal anti-inflammatory drugs (such as naproxen) leads to afferent arteriolar constriction and reduction in glomerular flow/pressure. Angiotensin II causes efferent arteriolar vasoconstriction. Blocking angiotensin II (with angiotensin-converting enzyme [ACE] inhibitors or angiotensin receptor blockers [ARBs]) can cause efferent arteriolar vasodilation and a decrement in glomerular flow/pressure. For this patient, both mechanisms are likely active. Patients with bilateral renal artery stenosis are particularly prone to reductions in glomerular filtration rate with ACE inhibitor or ARB therapy because they rely heavily on vasoconstriction of the efferent arterioles to maintain glomerular pressure.

I-119. The answer is E. *(Chap. 49)* This patient likely has osmotic demyelination syndrome (ODS) and central pontine myelinolysis due to the rapid correction of his chronic hyponatremia. The management of chronic hyponatremia is complicated significantly by the asymmetry of the cellular response to correction of plasma Na^+ concentration. Specifically, the *reaccumulation* of organic osmolytes by brain cells is attenuated and delayed as osmolality increases after correction of hyponatremia, sometimes resulting in degenerative loss of oligodendrocytes and an ODS. Overly rapid correction of hyponatremia (>8–10 m*M* in 24 hours or 18 m*M* in 48 hours) is also associated with a disruption in integrity of the blood-brain barrier, allowing the entry of immune mediators that may contribute to demyelination. The lesions of ODS classically affect the pons, a neuroanatomic structure wherein the delay in the reaccumulation of osmotic osmolytes is particularly pronounced. Clinically, patients with central pontine myelinolysis can present one or more days after overcorrection of hyponatremia with paraparesis or quadriparesis, dysphagia, dysarthria, diplopia, a "locked-in syndrome," and/or loss of consciousness. Other regions of the brain can also be involved in ODS, most commonly in association with lesions of the pons but occasionally in isolation; in order of frequency, the lesions of extrapontine myelinolysis can occur in the cerebellum, lateral geniculate body, thalamus, putamen, and cerebral cortex or subcortex. Clinical presentation of ODS can, therefore, vary as a function of the extent and localization of extrapontine myelinolysis, with the reported development of ataxia, mutism, parkinsonism, dystonia, and catatonia.

I-120. The answer is B. *(Chap. 49)* The patient in I-119 has osmotic demyelination syndrome (ODS) as a result of overly rapid correction of hyponatremia after presenting with chronic hyponatremia. Re-lowering of the plasma Na^+ concentration after overly rapid correction can prevent or may attenuate ODS. Thus, the intervention can be diagnostic and therapeutic. Albuminocytologic dissociation is a finding common in Guillain-Barré syndrome, but osmotic demyelination is a more likely cause of this patient's symptoms. Imaging of his lower spine would not demonstrate the typical findings of ODS, and high-dose steroids are not indicated.

I-121. The answer is D. *(Chap. 49)* Osmolality and water homeostasis are jealously guarded within the body. Vasopressin secretion, water ingestion, and renal water transport collaborate to maintain human body fluid osmolality between 280 and 295 mOsm/kg. Vasopressin (AVP) is synthesized in magnocellular neurons within the hypothalamus; the distal axons of these neurons project to the posterior pituitary or neurohypophysis, from which AVP is released into the circulation. A network of central "osmoreceptor" neurons, which includes the AVP-expressing magnocellular neurons themselves, sense circulating osmolality via nonselective, stretch-activated cation channels. These osmoreceptor neurons are activated or inhibited by modest increases and decreases in circulating osmolality, respectively; activation leads to AVP release and thirst. AVP secretion is stimulated as systemic osmolality increases above a threshold level of ~285 mOsm/kg, above which there is a linear relationship between osmolality and circulating AVP. Thirst and thus water ingestion are also activated at ~285 mOsm/kg, beyond which there is an equivalent linear increase in the perceived intensity of thirst as a function of circulating osmolality. The excretion or retention of electrolyte-free water by the kidney is modulated by circulating AVP. AVP acts on renal, V2-type receptors in the thick ascending limb of Henle (TALH) and principal cells of the collecting duct (CD), increasing intracellular levels of cyclic adenosine monophosphate and activating protein kinase A (PKA)-dependent phosphorylation of multiple transport proteins. The AVP- and PKA-dependent activation of Na^+-Cl^- and K^+ transport by the TALH is a key participant in the countercurrent mechanism, which ultimately increases the interstitial osmolality in the inner medulla of the kidney, driving water absorption across the renal CD. However, water, salt, and solute transport by both proximal and distal nephron segments participates in the renal concentrating mechanism. AVP-induced, PKA-dependent phosphorylation of the aquaporin-2 water channel in principal cells stimulates the insertion of active water channels into the lumen of the CD, resulting in transepithelial water absorption down the medullary osmotic gradient. Under "antidiuretic" conditions, with increased circulating AVP, the kidney reabsorbs water filtered by the glomerulus, equilibrating the osmolality across the CD epithelium to excrete a hypertonic, "concentrated" urine (osmolality of up to 1200 mOsm/kg). In the absence of circulating AVP, insertion of aquaporin-2 channels and water absorption across the CD are essentially abolished, resulting in secretion of a hypotonic, dilute urine (osmolality as low as 30–50 mOsm/kg). Abnormalities in this "final common pathway" are involved in most disorders of water homeostasis (e.g., a reduced or absent insertion of active aquaporin-2 water channels into the membrane of principal cells in diabetes insipidus).

I-122. **The answer is D**. *(Chap. 49)* This patient is dehydrated (hypovolemic) from vomiting and has a hypochloremic metabolic alkalosis because gastric secretions have a low pH (high H^+ concentration), whereas biliary, pancreatic, and intestinal secretions are alkaline (vomiting is typically accompanied by metabolic alkalosis and diarrhea by metabolic acidosis). The neurohumoral response to hypovolemia stimulates an increase in renal tubular Na^+ and water reabsorption, with a urine osmolality of >450 mOsm/kg. The reduction in both glomerular filtration rate and distal tubular Na^+ delivery may cause a defect in renal potassium excretion, with an increase in plasma K^+ concentration. Of note, patients with hypovolemia and a hypochloremic alkalosis due to vomiting or diuretics will typically have a urine Na^+ concentration >20 m*M* and urine pH of >7.0, due to the increase in filtered HCO_3^-; the urine Cl^- concentration in this setting is a more accurate indicator of volume status, with a level <25 m*M* suggestive of hypovolemia. Patients with uncomplicated hypovolemia, such as after insufficient oral intake or diarrhea, will have urine sodium <20 m*M* due to high aldosterone levels. The urine Na^+ concentration is also often >20 m*M* in patients with intrinsic renal injury. Urine specific gravity increases as osmolality increases; in this case, it would be elevated, or >1.020.

I-123. **The answer is E.** *(Chap. 49)* Largely, hyponatremia is due to a dyscrasia in water homeostasis. There are some conditions (e.g., beer potomania) in which very low intake of dietary solutes leads to hyponatremia, although antidiuretic hormone (ADH) levels are likely initially elevated in this condition (although they have never been measured). In most cases of hyponatremia (dehydration, heart failure, cirrhosis), the effective arterial circulating volume is reduced, leading to excess ADH signaling and water reabsorption. However, in psychogenic polydipsia, the patient drinks massive amounts of solute-free water, overwhelming the body's ability to excrete free water. In this setting, ADH is suppressed. Central diabetes insipidus is a failure of manufacture or release of ADH; thus, it is associated with a reduction in ADH levels. However, it is associated with hypernatremia.

I-124. **The answer is E.** *(Chap. 49)* This patient has pseudohyponatremia. Laboratory investigation should include a measurement of serum osmolality to exclude pseudohyponatremia, which is defined as the coexistence of hyponatremia with a normal or increased plasma tonicity. Most clinical laboratories measure plasma Na^+ concentration by testing diluted samples with automated ion-sensitive electrodes, correcting for this dilution by assuming that plasma is 93% water. This correction factor can be inaccurate in patients with pseudohyponatremia due to extreme hyperlipidemia and/or hyperproteinemia, in whom serum lipid or protein makes up a greater percentage of plasma volume. This patient likely has a type of familial hyperlipidemia associated with elevated triglycerides (thus explaining his seemingly idiopathic pancreatitis) and accounting for his pseudohyponatremia.

I-125. **The answer is E.** *(Chap. 49)* This patient has severe hypernatremia after being denied free water. In the state of nephrogenic diabetes insipidus, the kidneys fail to respond to ADH and excrete dilute urine regardless of serum osmolality. To correct this hyponatremia, you must first calculate the patient's total free water deficit. This is calculated as ([Na] – 140/140) × (total body water) where total body water is roughly 50–60% of body weight (60% in men, or 60 kg for Mr. Matherli). Thus, Mr. Matherli's free water deficit is ~8.5 L (or 8500 mL). To replace this in 24 hours requires approximately 350 mL/h of free water administration.

I-126. **The answer is A.** *(Chap. 50)* Disorders that directly increase calcium mobilization from bone, such as hyperthyroidism or osteolytic metastases, also lead to hypercalcemia with suppressed parathyroid hormone (PTH) secretion as does exogenous calcium overload,

TABLE I-126 Causes of Hypercalcemia

Excessive PTH production	Primary hyperparathyroidism (adenoma, hyperplasia, rarely carcinoma)
	Tertiary hyperparathyroidism (long-term stimulation of PTH secretion in renal insufficiency)
	Ectopic PTH secretion (very rare)
	FHH
	Alterations in CaSR function (lithium therapy)
Hypercalcemia of malignancy	Overproduction of PTHrP (many solid tumors)
	Lytic skeletal metastases (breast, myeloma)
Excessive $1,25(OH)_2D$ production	Granulomatous diseases (sarcoidosis, tuberculosis, silicosis)
	Lymphomas
	Vitamin D intoxication
Primary increase in bone resorption	Hyperthyroidism
	Immobilization
Excessive calcium intake	Milk-alkali syndrome
	Total parenteral nutrition
Other causes	Endocrine disorders (adrenal insufficiency, pheochromocytoma, VIPoma)
	Medications (thiazides, vitamin A, antiestrogens)

Abbreviations: CaSR, calcium sensor receptor; FHH, familial hypocalciuric hypercalcemia; PTH, parathyroid hormone; PTHrP, PTH-related peptide.

as in milk-alkali syndrome, or total parenteral nutrition with excessive calcium supplementation (Table I-126). With worsening bone pain and a history of lung cancer, which commonly metastasizes to the bone producing osteolytic bone metastases, this patient likely has hypercalcemia as the result of bone metastasis from his lung cancer. The causes of hypercalcemia can be understood and classified based on derangements in the normal feedback mechanisms that regulate serum calcium. Excess PTH production, which is not appropriately suppressed by increased serum calcium concentrations, occurs in primary neoplastic disorders of the parathyroid glands (parathyroid adenomas; hyperplasia; or, rarely, carcinoma) that are associated with increased parathyroid cell mass and impaired feedback inhibition by calcium. Although PTH secretion by tumors is extremely rare, many solid tumors produce PTH-related peptide (PTHrP), which shares homology with PTH in the first 13 amino acids and binds the PTH receptor, thus mimicking effects of PTH on bone and kidneys. In PTHrP-mediated hypercalcemia of malignancy, PTH levels are suppressed by the high serum calcium levels. Hypercalcemia associated with granulomatous disease (e.g., sarcoidosis) or lymphomas is caused by enhanced conversion of 25(OH)D to the potent $1,25(OH)_2D$. In these disorders, $1,25(OH)_2D$ enhances intestinal calcium absorption, resulting in hypercalcemia and suppressed PTH. When serum albumin concentrations are reduced, a corrected calcium concentration is calculated by adding 0.2 m*M* (0.8 mg/dL) to the total calcium level for every decrement in serum albumin of 1.0 g/dL below the reference value of 4.1 g/dL for albumin and, conversely, for elevations in serum albumin. His corrected serum calcium is still elevated at 13.3 (12.1 + [4 – 2.5] × 0.8).

I-127. The answer is B. *(Chap. 50)* When serum albumin concentrations are reduced, a corrected calcium concentration is calculated by adding 0.2 m*M* (0.8 mg/dL) to the total calcium level for every decrement in serum albumin of 1.0 g/dL below the reference value of 4.1 g/dL for albumin and, conversely, for elevations in serum albumin. For this patient, the corrected serum calcium is elevated at 12.7 (11.5 + [4 – 2.5] × 0.8). Significant symptomatic hypercalcemia usually requires therapeutic intervention independent of the etiology of hypercalcemia. Initial therapy of significant hypercalcemia begins with volume expansion because hypercalcemia invariably leads to dehydration; 4–6 L of IV saline may be required over the first 24 hours, keeping in mind that underlying comorbidities (e.g., congestive heart failure) may require the use of loop diuretics to enhance sodium and calcium excretion. However, loop diuretics should not be initiated until the volume status has been restored to normal. If there is increased calcium mobilization from bone (as in malignancy or severe hyperparathyroidism), drugs that inhibit bone resorption should be considered. Zoledronic acid (e.g., 4 mg IV over ~30 minutes), pamidronate (e.g., 60–90 mg IV over 2–4 hours), and ibandronate (2 mg IV over 2 hours) are bisphosphonates that are commonly used for the treatment of hypercalcemia of malignancy in adults. In patients with 1,25(OH)2D-mediated hypercalcemia, glucocorticoids are the preferred therapy, as they decrease 1,25(OH)2D production. IV hydrocortisone (100–300 mg daily) or oral prednisone (40–60 mg daily) for 3–7 days is used most often.

I-128. **The answer is D.** *(Chap. 50)* The first step in the diagnostic evaluation of hyper- or hypocalcemia is to ensure that the alteration in serum calcium levels is not due to abnormal albumin concentrations. About 50% of total calcium is ionized, and the rest is bound principally to albumin. Although direct measurements of ionized calcium are possible, they are easily influenced by collection methods and other artifacts; thus, it is generally preferable to measure total calcium and albumin to "correct" the serum calcium. When serum albumin concentrations are reduced, a corrected calcium concentration is calculated by adding 0.2 m*M* (0.8 mg/dL) to the total calcium level for every decrement in serum albumin of 1.0 g/dL below the reference value of 4.1 g/dL for albumin and, conversely, for elevations in serum albumin. This patient's albumin is 2.5, or ~1.5 below the reference value. Thus, you would add 1.6 (or 0.8 × 1.5) to the measured calcium level, arriving at a corrected value of 9.4 mg/dL—a value requiring no treatment for the hypocalcemia. Additional evaluation may be in order in this patient for his symptoms and reduced serum albumin.

I-129. **The answer is B.** *(Chap. 51)* This patient has evidence of an alkalosis with serum pH >7.45; thus, both choices with acidosis are ruled out. The next step is to evaluate which physiologic determinant of pH accounts for the alkalosis. The $PaCO_2$ is high (normal ~40mmHg); thus, it is not compatible with a respiratory alkalosis. The HCO_3^- is high, compatible with a metabolic alkalosis. The expected $PaCO_2 = 0.7[HCO_3^-] + 20 \pm 5$. In this case $0.7(32) + 20 \pm 5 = 42.4 \pm 5$ so the observed $PaCO_2$ is within this range. Metabolic alkalosis occurs as a result of net gain of $[HCO_3^-]$ or loss of nonvolatile acid (usually HCl by vomiting) from the extracellular fluid. When vomiting causes loss of HCl from the stomach, HCO_3^- secretion cannot be initiated in the small bowel and thus HCO_3^- is added to the extracellular fluid. Thus vomiting or nasogastric suction is an example of the *generation stage*, in which the loss of acid typically causes alkalosis. On cessation of vomiting, the *maintenance stage* typically ensues because secondary factors prevent the kidneys from compensating by excreting HCO_3^-. Maintenance of metabolic alkalosis, therefore, represents a failure of the kidneys to eliminate excess HCO_3^- from the extracellular compartment. The kidneys will retain, rather than excrete, the excess alkali and maintain the alkalosis if (1) volume deficiency, chloride deficiency, and K^+ deficiency exist in combination with a reduced glomerular filtration rate or (2) hypokalemia exists because of autonomous hyperaldosteronism. In this example, alkalosis is corrected by administration of NaCl and KCl, whereas, in the latter, it may be necessary to repair the alkalosis by pharmacologic or surgical intervention, not with saline administration.

I-130. **The answer is A.** *(Chap. 51)* This patient is suffering from ethylene glycol toxicity (ethylene glycol levels are likely in the additional tests that are pending). Ingestion of ethylene glycol (commonly used in antifreeze) leads to a metabolic acidosis and severe damage to the central nervous system, heart, lungs, and kidneys. The increased anion gap and osmolar gap are attributable to ethylene glycol, its metabolites oxalic acid and glycolic acid, and other organic acids. Lactic acid production increases secondary to inhibition of the tricarboxylic acid cycle and altered intracellular redox state. Diagnosis is facilitated by recognizing oxalate crystals in the urine, the presence of an osmolar gap in serum, and a high anion gap metabolic acidosis. Although use of a Wood lamp to visualize the fluorescent additive to commercial antifreeze in the urine of patients with ethylene glycol ingestion is suggested; this is rarely reproducible. The combination of a high anion gap and high osmolar gap in a patient suspected of ethylene glycol ingestion should be taken as evidence of ethylene glycol toxicity. This patient's osmolar gap is 20. Calculated serum osmolality is 2(Na) + BUN/2.8 + glucose/18 = 300 in this case. Therefore, the osmolar gap is 20 (320 – 300). Treatment should not be delayed while awaiting measurement of ethylene glycol levels in this setting. Treatment includes the prompt institution of a saline or osmotic diuresis, thiamine and pyridoxine supplements, fomepizole, and occasionally, hemodialysis. The IV administration of the alcohol dehydrogenase inhibitor fomepizole (4-methylpyrazole; 15 mg/kg as a loading dose) is the treatment of choice and offers the advantages of a predictable decline in ethylene glycol levels without excessive obtundation as seen during ethyl alcohol infusion. If used, ethanol IV should be infused to achieve a blood level of 22 mmol/L (100 mg/dL). Both fomepizole and ethanol reduce toxicity because they compete with ethylene glycol for metabolism by alcohol dehydrogenase. Hemodialysis is indicated when the arterial pH is <7.3 or the osmolar gap exceeds 20 mOsm/kg.

I-131. **The answer is E.** *(Chap. 52)* Figure I-131 shows vitiligo. Characteristic lesions display an acral distribution and striking depigmentation as a result of loss of melanocytes. A Wood lamp generates a 360-nm ultraviolet ("black") light that can be used to aid the evaluation of certain skin disorders. Vitiligo appears totally white under a Wood lamp, and previously unsuspected areas of involvement often become apparent. A potassium hydroxide preparation is performed on scaling skin lesions where a fungal infection is suspected. A Tzanck smear is a cytologic technique most often used in the diagnosis of herpes virus infections (herpes simplex virus or varicella zoster virus). Diascopy is designed to assess whether a skin lesion will blanch with pressure as, for example, in determining whether a red lesion is hemorrhagic or simply blood-filled. Diascopy is performed by pressing a microscope slide or magnifying lens against a lesion and noting the amount of blanching that occurs. Granulomas often have an opaque to transparent, brown-pink "apple jelly" appearance on diascopy.

I-132. **The answer is D.** *(Chap. 53)* In the absence of a bioterrorism attack and a real or potential exposure to smallpox, such vaccination is contraindicated in persons with a history of skin diseases such as atopic dermatitis, eczema, and psoriasis, who have a higher incidence of adverse events associated with smallpox vaccination. In the case of such exposure, the risk of smallpox infection outweighs that of adverse events from the vaccine. The other listed diseases are not contraindications to smallpox vaccine.

I-133. **The answer is D.** *(Chap. 53)* Examination shows hyperpigmentation, lichenification, and scaling in the antecubital fossae of this boy. These lesions are typical examples of childhood atopic dermatitis, the cutaneous expression of the atopic state. Over 75% of patients present by 5 years of age, and a similar proportion have concomitant asthma and/or allergic rhinitis. There is a strong genetic predisposition. Over 80% of children with both parents with atopic dermatitis will have similar skin findings; the prevalence is approximately 50% when one parent is affected. In addition to the antecubital fossae, the face, neck, and other extensor surfaces are commonly affected. The typical course involves exacerbations and remissions. In the adult form, the disease is often localized lichen simplex chronicus or hand eczema. Treatment of atopic dermatitis involves adequate moisturizing, topical anti-inflammatories, and avoidance of secondary bacterial infection. Topical tacrolimus and pimecrolimus are approved as therapy. They do not cause some of the complications of topical corticosteroids, but recent reports have raised the concern of a potentially increased risk of lymphoma. Children with atopic dermatitis may have spontaneous resolution, but about 40% of children with symptoms will have dermatitis as adults. Interestingly, for unknown reasons, the worldwide prevalence of atopic dermatitis is increasing.

I-134. **The answer is C.** *(Chap. 54)* In *pyoderma gangrenosum*, the border of untreated active ulcers has a characteristic appearance consisting of an undermined necrotic violaceous edge and a peripheral erythematous halo. The ulcers often begin as pustules that then expand rather rapidly to a size as large as 20 cm. Although these lesions are most commonly found on the lower extremities, they can arise anywhere on the surface of the body, including at sites of trauma (pathergy). An estimated 30–50% of cases are idiopathic, and the most common associated disorders are ulcerative colitis and Crohn disease. Administration of warfarin can result in painful areas of erythema that become purpuric and then necrotic with an adherent black eschar; the condition is referred to as warfarin-induced necrosis. This reaction is seen more often in women and in areas with abundant subcutaneous fat such as breasts, abdomen, buttocks, thighs, and calves. The erythema and purpura develop between the third and tenth day of therapy, most likely as a result of a transient imbalance in the levels of anticoagulant and procoagulant vitamin K–dependent factors. Erythema multiforme creates a reaction pattern of skin consisting of a variety of lesions but most commonly erythematous papules and bullae. A "target" or "iris" lesion is characteristic and consists of concentric circles of erythema and normal flesh-colored skin, often with a central vesicle or bulla. Purpura secondary to cholesterol emboli are usually seen on the lower extremities of patients with atherosclerotic vascular disease. They often follow anticoagulant therapy or an invasive vascular procedure such as an arteriogram but also occur spontaneously from disintegration of atheromatous plaques. Associated findings include livedo reticularis, gangrene, cyanosis, and ischemic ulcerations.

I-135. **The answer is A.** *(Chap. 54)* This patient presents with clinical characteristics consistent with telogen effluvium, a common cause of diffuse, nonscarring hair loss. Telogen effluvium occurs when typically asynchronous hair growth cycles become synchronous, therefore, a large number of hairs simultaneously change from a cycle of growth (anagen) to death (telogen). Common causes of telogen effluvium include stressors such as high fevers or infection, medications, and changes in hormone levels. The postpartum period is a common time when telogen effluvium occurs. On physical examination, a practitioner may not notice any visible hair thinning, although examination of pictures of the patient from prior to the onset may allow the changes to become clinically recognizable. More importantly, the clinician should not find evidence of broken or brittle hair or scalp changes, including scaling or scarring. The hair pull test may yield an increased number of intact hairs (>6–10) with light pressure. Telogen effluvium does not require any treatment and is reversible. Any potential offending medication should be stopped, and the patient should be examined for underlying metabolic disorders.

I-136. **The answer is D.** *(Chap. 55)* The examination shows violaceous, hyperpigmented, atrophic plaques; follicular plugging; and scarring that are typical features of chronic cutaneous lupus erythematosus (LE) or discoid LE (DLE). Biopsy of DLE lesions shows hyperkeratosis; follicular plugging; atrophy of the epidermis; hydropic degeneration of basal keratinocytes; thickening of the epidermal basement membrane zone; and a mononuclear cell infiltrate adjacent to epidermal, adnexal, and microvascular basement membranes. Direct immunofluorescence microscopy demonstrates immunoglobulin(s) and complement deposits at the basement membrane zone in ~90% of cases. Treatment is focused on control of local cutaneous disease and consists mainly of photoprotection and topical or intralesional glucocorticoids. If local therapy is ineffective, use of aminoquinoline antimalarial agents may be indicated. Intraepidermal vesicle formation secondary to loss of cohesion between epidermal cells (i.e., acantholytic blisters) is found in pemphigus vulgaris. Eosinophil-rich infiltrate at sites of vesicle formation and in perivascular areas is typical of bullous pemphigoid. In addition to eosinophils, cell-rich lesions also contain mononuclear cells and neutrophils.

I-137. **The answer is A.** *(Chap. 55)* Bullous pemphigoid is an autoimmune cutaneous disease that primarily presents in elderly individuals. Although the initial lesions may consist of urticarial plaques, most patients eventually develop tense blisters on either a normal or erythematous base. Typical lesions of bullous pemphigoid are demonstrated in this patient. The most common sites of bullous pemphigoid are the lower abdomen, groin, and flexor surfaces of the extremities. Oral mucosal lesions may be seen but are not the common presenting lesion that is typically seen in pemphigus vulgaris. Pruritus may or may not be present. However, if present, it may be severe. Nontraumatized blisters will heal without scarring. It should be noted that there is no epidemiologic link between bullous pemphigoid and undiagnosed malignancy despite some initial case studies suggesting this might be so. Biopsies of the lesions of bullous pemphigoid demonstrate a subepidermal blister with a dense eosinophil-rich infiltrate. Mononuclear cells and neutrophils are also seen. Biopsies of normal-appearing skin will also show minimal perivascular leukocytic infiltrate with some eosinophils. Direct immunofluorescence microscopy of normal appearing skin, however, will demonstrate linear deposits of IgG and/or C3 in the epidermal basement membrane, and about 70% of individuals with bullous pemphigoid have IgG autoantibodies that bind the epidermal basement membrane of normal human skin in indirect immunofluorescence microscopy. Bullous pemphigoid may persist for many months to years, with relapses and remissions. Most patients are treated with oral glucocorticoids. Additional immunosuppression may be needed in extensive disease.

I-138. **The answer is D.** *(Chap. 55)* Dermatitis herpetiformis (DH) is an immunologic skin disorder characterized by severe pruritus with skin lesions symmetrically distributed along the extensor surfaces, buttocks, back, scalp, and posterior neck. The lesions of DH may be papular, papulovesicular, or urticarial plaques. Because of the severity of the associated pruritus, many patients do not exhibit the primary skin lesions but have excoriations and crusted papules. Burning and stinging are also frequently reported along with the pruritus, and these symptoms are present prior to the manifestation of skin lesions. Almost all patients have an associated gluten-sensitive enteropathy, although it may be clinically unrecognized on presentation. Pathologically, the lesions demonstrate a neutrophilic inflammatory infiltrate in the dermal papillae. On immunofluorescence, granular deposits of IgA are found in the papillary dermis and along the epidermal basement membrane. The primary treatment of DH is dapsone at doses of 50–200 mg daily, with most patients reporting remarkable improvement within 24–48 hours. At doses greater than 100 mg daily, one must pay close attention to side effects because methemoglobinemia and hemolysis frequently occur. In addition to dapsone, gluten-free diets are recommended. However, many months of the diet are required to achieve a clinical benefit, so diet is not recommended as the sole treatment. Corticosteroids are not used in the treatment of DH.

I-139. **The answer is A.** *(Chap. 56)* In a series of 48,005 inpatients over a 20-year period, morbilliform rash (91%) and urticaria (6%) were the most frequent skin reactions (Figure I-139). Morbilliform or maculopapular eruptions are the most common of all drug-induced reactions, often start on the trunk or intertriginous areas, and consist of blanching erythematous macules and papules that are symmetric and confluent. Involvement of mucous membranes is rare and should prompt consideration of Stevens-Johnson syndrome. Severe reactions are too rare to be detected in such cohorts. Although rare, severe cutaneous reactions to drugs have an important impact on health because of significant sequelae, including mortality. Diagnosis of morbilliform eruptions is rarely assisted by laboratory testing. Skin biopsy often shows nonspecific inflammatory changes. Adverse drug rashes are responsible for hospitalization, increase the duration of hospital stay, and can be life-threatening.

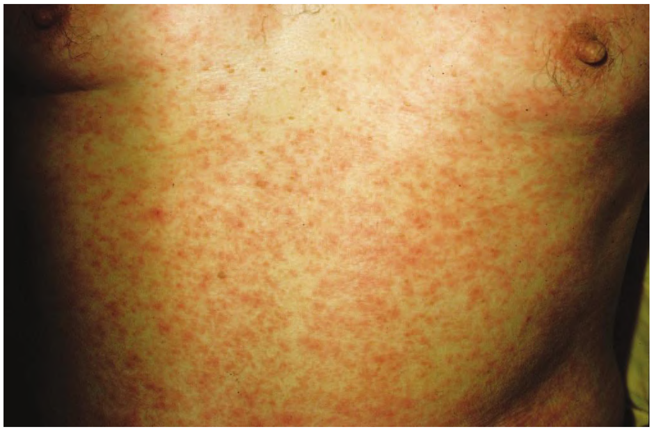


FIGURE I-139 Morbilliform drug eruption.

I-140. The answer is E. *(Chap. 57)* The porphyrins circulate in the bloodstream and diffuse into the skin, where they absorb solar energy, become photoexcited, generate reactive oxygen species (ROS), and evoke cutaneous photosensitivity. The mechanism of porphyrin photosensitization is known to be photodynamic, or oxygen dependent, and is mediated by ROS such as singlet oxygen and superoxide anions. Lupus is also associated with photosensitivity and antinuclear antibodies and anti-Ro and anti-La antibodies are helpful in that diagnosis. Vitamin D levels may be affected by sun exposure but are not helpful in determining the cause of photosensitivity (Figure I-140).

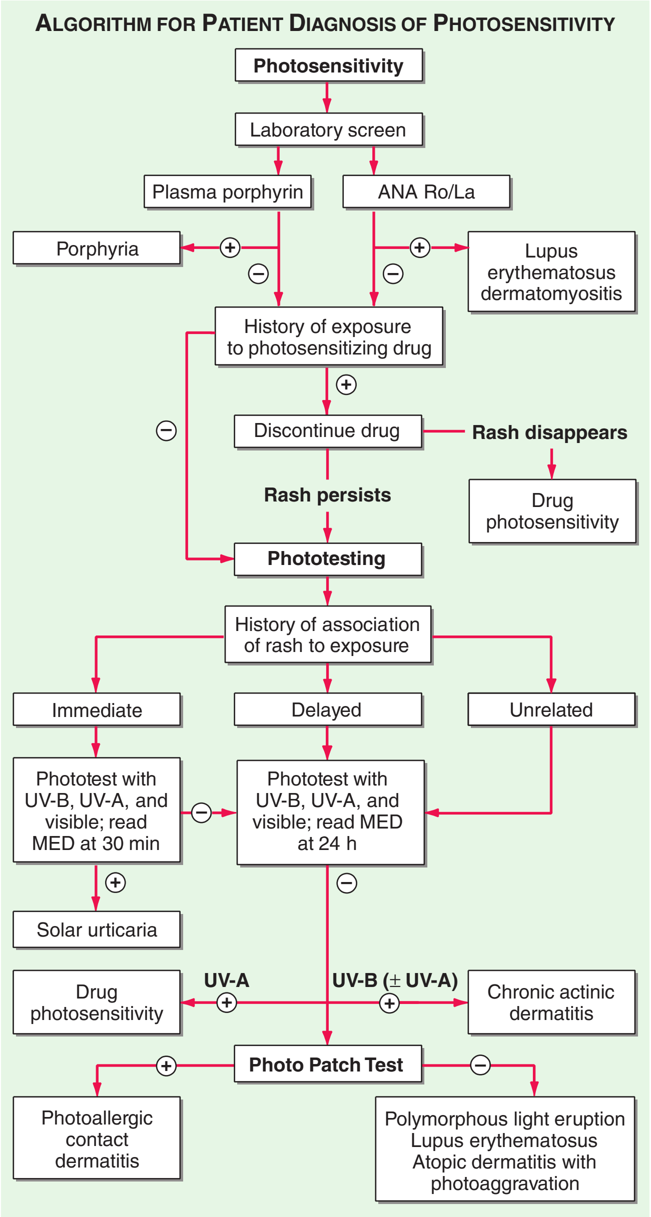

ALGORITHM FOR PATIENT DIAGNOSIS OF PHOTOSENSITIVITY
Photosensitivity
Laboratory screen
Plasma porphyrin
ANA Ro/La
Porphyria
+
−
+
−
Lupus erythematosus dermatomyositis
History of exposure to photosensitizing drug
+
−
Discontinue drug
Rash disappears
Rash persists
Drug photosensitivity
Phototesting
History of association of rash to exposure
Immediate
Delayed
Unrelated
Phototest with UV-B, UV-A, and visible; read MED at 30 min
−
Phototest with UV-B, UV-A, and visible; read MED at 24 h
+
−
Solar urticaria
Drug photosensitivity
UV-A
+
UV-B (± UV-A)
+
Chronic actinic dermatitis
+
Photo Patch Test
−
Photoallergic contact dermatitis
Polymorphous light eruption Lupus erythematosus Atopic dermatitis with photoaggravation

FIGURE I-140 *Abbreviations:* ANA, antinuclear antibody; MED, minimal erythemal dose; UV-A, UV-B, ultraviolet A and B.

I-141. The answer is C. *(Chap. 57) Phototoxicity* is a nonimmunologic reaction that can be caused by a broad range of drugs and chemicals. The usual clinical manifestations include erythema resembling a sunburn reaction that quickly desquamates, or "peels," within several days. In addition, edema, vesicles, and bullae may occur. *Photoallergy* is much less common and is distinct in that it is an immunopathologic process. The excited-state photosensitizer may create highly unstable haptenic free radicals that bind covalently to macromolecules to form a functional antigen capable of evoking a delayed-type

TABLE I-141 Drugs That May Cause a Photoallergic Reaction

Drug	Topical	Systemic
6-Methylcoumarin	+	
Aminobenzoic acid and esters	+	
Bithionol	+	
Chlorpromazine		+
Diclofenac		+
Fluoroquinolones		+
Halogenated salicylanilides	+	
Hypericin (St. John's wort)	+	+
Musk ambrette	+	
Piroxicam		+
Promethazine		+
Sulfonamides		+
Sulfonylureas		+

hypersensitivity response. Thiazides are associated with phototoxic reactions while the other medications listed in Table I-141 are associated with photoallergies.

I-142. **The answer is B.** *(Chap. 58)* Normal red blood cells are similar in size to normal small lymphocytes. Both are normally about 8 µm wide. Neutrophils are 10–14 µm wide. In the presence of viral infections, more of the lymphocytes are larger, about the size of neutrophils, with abundant cytoplasm and a less condensed nuclear chromatin. These cells are called *reactive lymphocytes*. The platelets are usually 1–2 µm in diameter. Eosinophils are slightly larger than neutrophils.

I-143. **The answer is D.** *(Chap. 58)* The smear in Figure I-143 shows hypersegmented neutrophils (multilobed polymorphonuclear leukocytes), which are larger than normal neutrophils with five or more segmented nuclear lobes. They are commonly seen with folic acid or vitamin B_{12} deficiency. Vacuolated neutrophils or bands (immature neutrophils that have not completed nuclear condensation and have a U-shaped nucleus) may be a sign of bacterial sepsis. In acute myeloid leukemia, you would expect to see a uniform population of primitive myeloblasts with immature chromatin, nucleoli in some cells, and primary cytoplasmic granules. In chronic lymphoid leukemia, the small lymphocytes are increased in number, and many of them are ruptured in making the blood smear, leaving a smudge of nuclear material without a surrounding cytoplasm or cell membrane; they are called *smudge cells* and are rare in the absence of chronic lymphoid leukemia.

I-144. **The answer is C.** *(Chap. 59)* This patient is presenting with iron-deficiency anemia. The peripheral blood smear in Figure I-144A shows microcytic and hypochromic red cells smaller than the nucleus of a lymphocyte associated with marked variation in size (anisocytosis) and shape (poikilocytosis). With chronic anemia, intracellular levels of 2,3-bisphosphoglycerate rise, shifting the dissociation curve to the right and facilitating O_2 unloading. This compensatory mechanism can only maintain normal tissue O_2 delivery in the face of a hemoglobin concentration deficit of 20–30 g/L (2–3 g/dL). When the hemoglobin concentration falls below 100–120 g/L (10–12 g/dL), plasma erythropoietin (EPO) levels increase in proportion to the severity of the anemia (Figure I-144B). EPO acts by binding to specific receptors on the surface of marrow erythroid precursors, inducing them to proliferate and to mature. Key to EPO gene regulation is hypoxia-inducible factor (HIF)-1α. In the presence of O_2, HIF-1α is hydroxylated at a key proline, allowing HIF-1α to be ubiquitinated and degraded via the proteasome pathway. If O_2 becomes limiting, this critical hydroxylation step does not occur, allowing HIF-1α to partner with other proteins, translocate to the nucleus, and upregulate the expression of the EPO gene, among others. Therefore, both EPO and HIF-1α would be expected to be increased. Given the lack of nutrients (iron in this case), the reticulocyte count would not be appropriately increased for the degree of anemia.

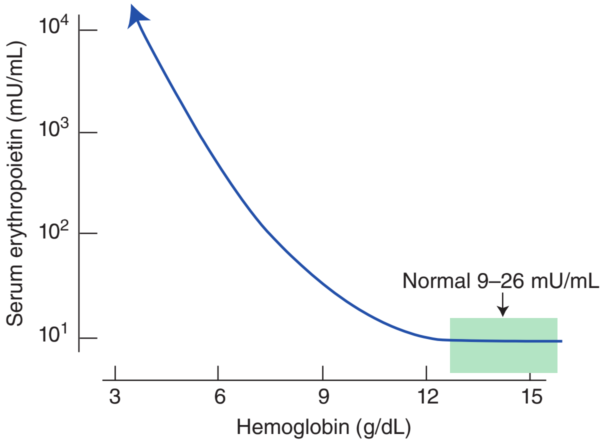


FIGURE I-144B Reproduced with permission from Hillman RS et al: *Hematology in Clinical Practice*, 5th ed. New York: McGraw Hill, 2010.

I-145. **The answer is B.** *(Chap. 59)* Sickle cell disease results in a microcytic or normocytic, normochromic anemia and is characterized by complications related to sickling of red blood cells (RBCs) in capillaries throughout the body. Intermittent episodes of vaso-occlusion in connective and musculoskeletal structures produce ischemia manifested by acute pain and tenderness, fever, tachycardia, and anxiety. These recurrent episodes, called *painful crises*, are the most common clinical manifestation. Repeated microinfarction can destroy tissues having microvascular beds prone to sickling. Thus, splenic function is frequently lost within the first 18–36 months of life. In the absence of a functional spleen, nuclear remnants are not culled from the red cells and remain as small homogeneously staining blue inclusions on a Wright stain, called Howell-Jolly bodies. Burr cells are typically seen in uremia and show multiple spiny projections. Schistocytes are helmet-shaped cells that reflect microangiopathic hemolytic anemia or fragmentation on an artificial heart valve. These are commonly seen in disseminated intravascular coagulation. Spherocytes are small dense RBCs that lack central pallor and biconcavity. They are typically seen in hereditary spherocytosis but can also be seen in other autoimmune hemolytic anemias. Target cells have a bull's-eye appearance and are seen in thalassemia and in liver disease.

I-146. **The answer is A.** *(Chap. 59)* Patients with polycythemia may be asymptomatic or experience symptoms related to the increased red cell mass or the underlying disease process that leads to the increased red cell mass. The dominant symptoms from an increased red cell mass are related to hyperviscosity and thrombosis (both venous and arterial), because the blood viscosity increases logarithmically at hematocrits >55%. Manifestations include neurologic symptoms such as vertigo, tinnitus, headache, and visual disturbances. Hypertension is often present. The first step in the evaluation of polycythemia is to document the presence of an increased red cell mass using the principle of isotope dilution by administering ^{51}Cr-labeled autologous red blood cells to the patient and sampling blood radioactivity over a 2-hour period. If the red cell mass is normal (<36 mL/kg in men, <32 mL/kg in women), the patient has spurious or relative polycythemia. If the red cell mass is increased (>36 mL/kg in men, >32 mL/kg in women), serum erythropoietin (EPO) levels should be measured. If EPO levels are low or unmeasurable, the patient most likely has polycythemia vera (option B). If serum EPO levels are elevated, one needs to distinguish whether the elevation is a physiologic response to hypoxia or related to autonomous EPO production. Patients with low arterial O_2 saturation (<92%) should be further evaluated for the presence of heart or lung disease, if they are not living at high altitude. Patients with normal O_2 saturation who are smokers may have elevated EPO levels because of carbon monoxide (CO) displacement of O_2. If carboxyhemoglobin (COHb) levels are high, the diagnosis is "smoker's polycythemia." Such patients should be urged to stop smoking. Those who cannot stop smoking require phlebotomy to control their polycythemia.

I-147. **The answer is B.** *(Chap. 60)* The blood smear in Figure I-147 demonstrated large granules in neutrophils consistent with the Chédiak-Higashi syndrome (CHS). CHS is a rare disease with autosomal recessive inheritance due to defects in the lysosomal transport protein LYST, encoded by the gene *CHS1* at 1q42. This protein is required for normal packaging and disbursement of granules. Neutrophils (and all cells containing lysosomes) from patients with CHS characteristically have large granules, making it a systemic disease. Patients with CHS have nystagmus, partial oculocutaneous albinism, and an increased number of infections resulting from many bacterial agents. Some CHS patients develop an "accelerated phase" in childhood with a hemophagocytic syndrome and an aggressive lymphoma requiring bone marrow transplantation. CHS neutrophils and monocytes have impaired chemotaxis and abnormal rates of microbial killing due to slow rates of fusion of the lysosomal granules with phagosomes. Natural killer (NK) cell function is also impaired. CHS patients may develop a severe disabling peripheral neuropathy in adulthood. In the Pelger-Hüet anomaly, a benign disorder, the majority of granulocytes are bilobed. The nucleus frequently has a spectacle-like, or "pince-nez," configuration. Kostmann syndrome (neutrophil count <100/μL), is near complete absence of neutrophils and neutrophil precursors, which is often fatal and due to mutations in the antiapoptosis gene HAX-1. The smear in acute leukemia contains uniform population of primitive myeloblasts with immature chromatin, nucleoli in some cells, and primary cytoplasmic granules.

I-148. **The answer is E.** *(Chap. 60)* Many drugs can lead to neutropenia, most commonly via retarding neutrophil production in the bone marrow. Of the drugs listed in the question, trimethoprim-sulfamethoxazole is the most likely culprit. Other common causes of drug- induced neutropenia include alkylating agents such as cyclophosphamide or busulfan, antimetabolites including methotrexate and 5-flucytosine, penicillin and sulfonamide antibiotics, antithyroid drugs, antipsychotics, and anti-inflammatory agents. Prednisone, when used systemically, often causes an increase in the circulating neutrophil count because it leads to demargination of neutrophils and bone marrow stimulation. Ranitidine, an H_2 blocker, is a well-described cause of thrombocytopenia but has not been implicated in neutropenia. Efavirenz is a nonnucleoside reverse transcriptase inhibitor whose main side effects include a morbilliform rash and central nervous system effects including strange dreams and confusion. The presence of these symptoms does not require drug cessation. Darunavir is a protease inhibitor that is well tolerated. Common side effects include a maculopapular rash and lipodystrophy, a class effect for all protease inhibitors.

I-149. **The answer is B.** *(Chap. 61)* The platelet glycoprotein (Gp) IIb/IIIa ($\alpha_{IIb}\beta_3$) complex is the most abundant receptor on the platelet surface. Platelet activation converts the normally inactive Gp IIb/IIIa receptor into an active receptor, enabling binding to fibrinogen and von Willebrand factor (vWF). Because the surface of each platelet has about 50,000 Gp IIb/IIIa–binding sites, numerous activated platelets recruited to the site of vascular injury can rapidly form an occlusive aggregate by means of a dense network of intercellular fibrinogen bridges. Because this receptor is the key mediator of platelet aggregation, it has become an effective target for antiplatelet therapy. The vWF is a very large multimeric protein that is found in both the plasma and in the extracellular matrix of the subendothelial vessel wall. Platelet adhesion also occurs to a lesser degree with subendothelial collagen through specific platelet membrane collagen receptors. Tissue factor binds the cofactor VIIa and can act to directly activate factor X, or it can activate factor IX, which in turn acts with factor VIIIa to activate factor X. Activated factor X then converts prothrombin to thrombin, which in turn has a positive feedback on the coagulant system by activating factor XI (the classic intrinsic pathway). Protein C is a plasma glycoprotein that is activated by thrombin and acts to inactivate factors V and VIII.

I-150. **The answer is E.** *(Chap. 61)* This individual has experienced significant bleeding that is primarily mucosal in origin (postpartum hemorrhage, prior oral bleeding). This suggests a disorder of primary hemostasis, or platelet plug formation. von Willebrand disease (vWD) is the only disease listed that is a disorder of primary hemostasis. Bleeding symptoms that are common in vWD include prolonged bleeding after surgery, including dental procedures, menorrhagia, postpartum hemorrhage, and large bruises or hematomas, even with minor trauma. Epistaxis is also common but occurs in many other diseases as well. Therefore, a clinician should assess for other symptoms prior to ascribing the symptom to a disorder of platelet function. The postpartum hemorrhage can be delayed beyond the immediate period of delivery. Hemarthroses are rare in vWD unless the disease is very severe. All of the other disorders listed affect anticoagulant levels.

I-151. **The answer is C.** *(Chap. 61)* The most important part of determining bleeding risk prior to surgery is a careful history and physical examination. Routine testing for preoperative evaluation should include a prothrombin time because this test may detect a previously unknown vitamin K deficiency or unsuspected liver disease. Although it is common to concomitantly assess the activated partial thromboplastin time, the utility of this practice has not been validated in patients undergoing surgery in the absence of a bleeding history. The bleeding time has previously been used to assess bleeding risk but has not been shown to have any predictive value in determining individuals at increased bleeding risk during surgery. Thus, it should not be ordered.

I-152. **The answer is A.** *(Chap. 61)* Deciding which individuals require workup for hypercoagulability and the timing of the workup is a difficult diagnostic dilemma. This scenario presents an individual with two clotting episodes separated in time by a prolonged period and with clear risk factors. It is not likely that she would have a hypercoagulable state and therefore would not require further workup. However, limited testing could be performed at this point. Laboratory assays for thrombophilia include both molecular diagnostics for inherited risk factors for thrombophilia as well as immunologic and functional assays. Molecular diagnostics are not indicated in the absence of a strong family history of thrombosis. Levels of coagulation factors are affected by acute thrombosis, acute illness, inflammatory conditions, pregnancy, and medications. Antithrombin levels are decreased by heparin and in the setting of acute thrombosis. Protein C and S levels are decreased by warfarin and increased in the setting of acute thrombosis. Antiphospholipid antibody levels may even be transiently positive in acute illness. In most instances of acute thrombosis, anticoagulation with warfarin would be continued for 3–6 months. If a decision is made to perform a workup for a hypercoagulable state, it can be done at least 3 weeks after discontinuation of warfarin.

I-153. **The answer is D.** *(Chap. 62)* Splenectomy is infrequently performed for diagnostic purposes, especially in the absence of clinical illness or other diagnostic tests that suggest underlying disease. More often, splenectomy is performed for symptom control in patients with massive splenomegaly, for disease control in patients with traumatic splenic rupture, or for correction of cytopenias in patients with hypersplenism or immune-mediated destruction of one or more cellular blood elements. Splenectomy is necessary for staging of patients with Hodgkin disease only in those with clinical stage I or II disease in whom radiation therapy alone is contemplated as the treatment. Noninvasive staging of the spleen in Hodgkin disease is not a sufficiently reliable basis for treatment decisions because one-third of normal-sized spleens will be involved with Hodgkin disease and one-third of enlarged spleens will be tumor free. Although splenectomy in chronic myeloid leukemia (CML) does not affect the natural history of disease, removal of the massive spleen usually makes patients significantly more comfortable and simplifies their management by significantly reducing transfusion requirements. The improvements in therapy of CML have reduced the need for splenectomy for symptom control. In sickle cell anemia, patients usually become functionally asplenic but do not typically get prophylactic splenectomies. Passive congestion of the spleen due to portal hypertension is also a common cause of splenomegaly, and removal of the spleen will not treat the portal hypertension.

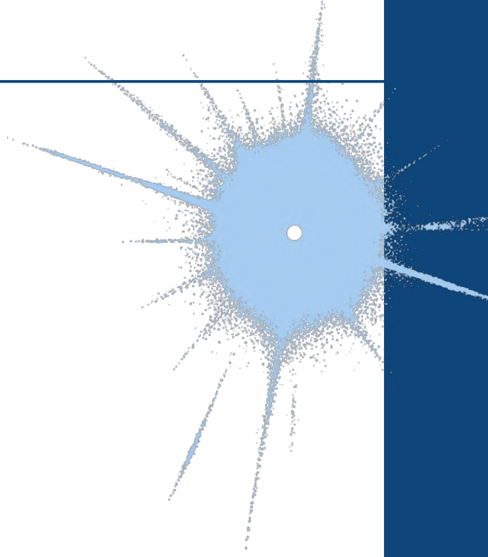
I-154. **The answer is D.** *(Chap. 62)* The absence of the spleen has minimal long-term effects on the hematologic profile. In the immediate postsplenectomy period, leukocytosis (up to 25,000/μL) and thrombocytosis (up to 1×10^6/μL) may develop, but within 2–3 weeks, blood cell counts and survival of each cell lineage are usually normal. The chronic manifestations of splenectomy are marked variation in size and shape of erythrocytes (anisocytosis, poikilocytosis) and the presence of Howell-Jolly bodies (nuclear remnants), Heinz bodies (denatured hemoglobin), basophilic stippling, and an occasional nucleated erythrocyte in the peripheral blood. The most serious consequence of splenectomy is increased susceptibility to bacterial infections, particularly those with capsules such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and some gram-negative enteric organisms. No increased risk of viral infection has been noted in patients who have no spleen.

I-155. **The answer is E.** *(Chap. 62)* Evaluation of enlarged lymph nodes is a common reason for evaluation in a primary care practice. Most of the time, the cause of an enlarged lymph node is benign. In one study, 84% of patients were found to have benign causes of lymphadenopathy, and only 16% had malignancy. Moreover, in more than half of the cases, the lymphadenopathy was deemed to be "reactive," and no specific cause was identified. When evaluating an individual for lymphadenopathy, a careful history and physical examination often provides clues to whether the individual is at risk for a malignant cause of disease. Children and young adults usually have benign causes of lymphadenopathy, including viral or bacterial upper respiratory tract infections, infectious mononucleosis, toxoplasmosis, or tuberculosis. After the age of 50, however, the incidence of malignant disorders increases. Other factors in medical history that favor a benign diagnosis include sore throat, cough, fever, night sweats, and fatigue. Localized or regional lymphadenopathy implies involvement of a single anatomic area, whereas generalized lymphadenopathy involves three or more noncontiguous lymph node areas. Many etiologies of lymphadenopathy can cause either localized/regional or generalized lymphadenopathy, so the distinction is of limited utility in determining benign from malignant disorders. Size, texture, and the presence of pain can be helpful in assessing whether a lymph node may be malignant, and size is often the most useful of these. Lymph nodes that are <1 cm in size are almost always due to benign causes, whereas size >2–2.25 cm carries a much greater likelihood of malignancy or granulomatous disease. If the size is ≤1 cm, then watchful waiting is prudent. When describing the texture of a lymph node, typical descriptions include *soft, firm, rubbery, hard, discrete, matted, tender, movable*, or *fixed*. It can be difficult to use these terms to distinguish benign from malignant disease by description alone, specifically in the case of lymphoma. Lymphomatous lymph nodes are most often firm, rubbery, discrete, and mobile. Depending on the rapidity of enlargement, they may or may not be tender. In comparison, lymph nodes in infection or infectious mononucleosis appear similarly but are frequently tender. However, metastatic lymph nodes often feel distinctly different. They are often hard, fixed, and nontender. In this patient, the diagnosis was most likely a benign case of infectious mononucleosis with the only concerning factor being a single lymph node that is 2 cm in size. A simple blood test will provide a diagnostic answer, but you would want to follow up the lymph node to ensure that the size diminished as the patient healed from her disease.

I-156. **The answer is A.** *(Chap. 62)* The presence of Howell-Jolly bodies (nuclear remnants), Heinz bodies (denatured hemoglobin), basophilic stippling, and nucleated red blood cells in the peripheral blood implies that the spleen is not properly clearing senescent or damaged red blood cells from the circulation. This usually occurs because of surgical splenectomy but is also possible when there is diffuse infiltration of the spleen with malignant cells. Hemolytic anemia can have various peripheral smear findings depending on the etiology of the hemolysis. Spherocytes and bite cells are an example of damaged red cells that might appear due to autoimmune hemolytic anemia and oxidative damage, respectively. Disseminated intravascular coagulation is characterized by schistocytes and thrombocytopenia on the peripheral blood smear, with elevated international normalized ratio and activated partial thromboplastin time as well. However, in these conditions, damaged red cells are still cleared effectively by the spleen. Transformation to acute leukemia does not lead to splenic damage.

SECTION II

Oncology and Hematology



QUESTIONS

DIRECTIONS: Choose the one best response to each question.

II-1. Which of the following is the most significant risk factor for cancer?

A. Age
B. Family history
C. Obesity
D. Tobacco

II-2. Mr. Borr is a 66-year-old man, recently diagnosed with multiple myeloma after presenting with fatigue from anemia and lower back pain. Further evaluation found malignant bone lesions in his thoracic and lumbar spine. He was started on multi-agent treatment 6 weeks ago and comes in for follow-up. He has been feeling well with decreased pain and denies any new side effects from treatment. He wants to know if his disease is responding to the current therapy. Which test would be the most helpful in assessing his response to treatment?

A. Complete blood count
B. Fluorodeoxyglucose-positron emission tomography scan
C. Flow cytometry
D. Lactate dehydrogenase
E. Monoclonal immunoglobulin

II-3. In recent decades, many cancer mortality rates are decreasing in men and women. Which of the following cancers, in fact, had an increasing mortality in recent years?

A. Colorectal cancer
B. Liver cancer
C. Lung cancer
D. Prostate cancer in men
E. Stomach cancer

II-4. A 68-year-old woman is diagnosed with stage II breast cancer. She has a history of severe chronic obstructive pulmonary disease with a FEV_1 of 32% predicted, coronary artery disease with prior stenting of the left anterior descending artery, peripheral vascular disease, and obesity. She continues to smoke one to two packs of cigarettes every day. She requires oxygen at 2 L/min continuously and is functionally quite limited. She currently is able to attend to all of her activities of daily living, including showering and dressing. She retired from her work as a waitress 10 years previously due to her lung disease. At home, she does perform some of the household chores but is not able to use a vacuum. She does go out once or twice weekly to run typical errands and does drive. She feels short of breath with most of these activities and often uses a motorized cart when out and about. How would you categorize her performance status and prognosis for treatment taking this into consideration?

A. She has an Eastern Cooperative Oncology Group (ECOG) performance status of 1 and has a good prognosis with appropriate therapy.
B. She has an ECOG performance status of 2 and has a good prognosis with appropriate therapy.
C. She has an ECOG performance status of 3 and has a good prognosis with appropriate therapy.
D. She has an ECOG performance status of 3 and has a poor prognosis despite therapy.
E. She has an ECOG performance status of 4 and has a poor prognosis that precludes therapy.

II-5. Which of the following screening tests is recommended in the patient described below?

A. A 44-year-old man with no family history of colon cancer: fecal occult blood test.
B. A 56-year-old woman at average risk of breast cancer: mammography every other year.
C. A 66-year-old woman at average risk of cervical cancer, with no prior history of cervical cancer or abnormal Pap smears: Pap screening every 3 years.
D. A 70-year-old man, former smoker who smoked 2 packs of cigarettes a day for 30 years, who quit smoking at age 60: annual chest x-ray.
E. A 74-year-old man with dysuria, hematuria, and urinary frequency and urgency: prostate-specific antigen testing.

II-6. You have developed a new screening test for disease X. When you compare your test to the gold standard test, you find that you are correctly able to identify 8 of 10 people who have the disease. You next test a population of 50 people without the disease and you identify 3 positive results on your test. Which of the following is true regarding your test?

A. The sensitivity is 20%.
B. The sensitivity is 94%.
C. The specificity is 6%.
D. The specificity is 94%.
E. It is impossible to calculate as you do not have the prevalence of the disease in the population.

II-7. All of the following are common genetic alterations seen in cancers EXCEPT:

A. Aneuploidy
B. Epigenetic modifications
C. Indels in oncogenes
D. Large deletions in tumor suppressor genes
E. Point mutations in oncogenes

II-8. A 39-year-old man comes to your clinic for his annual routine physical. He reports no new symptoms. He recently saw a commercial about genetic testing and asks for genetic testing to determine his risk of cancer. He has no personal history of cancer. His paternal grandfather, a heavy smoker and coal miner, died at the age of 74 of lung cancer. He has no other family history of cancer. What do you tell him regarding genetic testing for cancer risk?

A. Yes, given your family history, genetic testing would be recommended.
B. Yes, given your age, genetic testing would be recommended.
C. No, because you are not old enough for genetic testing.
D. No, because you do not have a familial cancer syndrome.
E. No, because you have not started cancer screening yet.

II-9. All of the following are mechanisms for cancer cells to evade the immune system EXCEPT:

A. Cell signaling disruption
B. Elaboration of immunosuppression of cytokines
C. Induction of cytotoxic T-lymphocyte-associated protein 4
D. T regulatory cell downregulation
E. Upregulation of macrophages

II-10. Ms. Jackson is a 69-year-old woman with metastatic thyroid cancer. Her cancer is progressing now after three different therapies. Her oncologist recommends that she join a clinical trial. After searching on the Internet, she finds a trial that she is eligible for and sounds interesting. The trial is testing a new drug, drug x. The main end point of the trial is to determine the maximally tolerated dose of drug x. What phase of drug development is drug x currently in?

A. Phase I
B. Phase II
C. Phase III
D. Phase IV

II-11. A 24-year-old woman is seen in follow-up 12 months after an allogeneic stem cell transplantation for acute myeloid leukemia. She is doing well without evidence of recurrent disease but has had manifestations of chronic graft-versus-host disease. She should be administered all of the following vaccines EXCEPT:

A. Diphtheria-tetanus-pertussis
B. Human papillomavirus
C. Poliomyelitis via injection
D. Seasonal influenza vaccine
E. Varicella-zoster virus

II-12. A 47-year-old man with no history of smoking or alcohol use is undergoing concurrent chemotherapy/radiation for head and neck cancer. He has been neutropenic for 2 days and develops a fever to 39.5°C (103°F). He also reports lightheadedness and shortness of breath. His blood pressure is 95/60, respiratory rate 28 breaths/min, and O_2 sat 95% on room air. What is the most appropriate therapy for this patient?

A. Start broad-spectrum oral antibiotics, continue until afebrile, and follow up as an outpatient in 1 week.
B. Start broad-spectrum oral antibiotics, continue until neutropenia resolves, and follow up as an outpatient in 1 week.
C. Admit to inpatient, start broad-spectrum oral antibiotics, and continue treatment until a source is found.
D. Admit to inpatient, start broad-spectrum IV antibiotics, and continue until neutropenia resolves.
E. Admit to inpatient, start broad-spectrum IV antibiotics, and continue treatment until afebrile.

II-13. A 63-year-old man is treated with paclitaxel and carboplatin chemotherapy for stage IIIB adenocarcinoma of the lung. He presents for evaluation of a fever to 38.3°C (100.9°F). He is found to have erythema at the exit site of his tunneled catheter, although the tunnel itself is not tender or red. Blood cultures are negative at 48 hours. His neutrophil count is 1550/μL. What is the best approach to the management of this patient?

A. Removal of catheter alone
B. Treatment with ceftazidime and vancomycin
C. Treatment with topical antibiotics at the catheter site
D. Treatment with vancomycin alone
E. Treatment with vancomycin and removal of catheter

II-14. A 68-year-old woman presents to the emergency room for shortness of breath. Her symptoms started 1 week ago and have been gradually progressive to the point she finds it difficult to catch her breath even at rest. She was seen by her primary care physician about 1 week ago when the symptoms were less severe. Chest x-ray at the time revealed “a spot on my lungs.” On physical examination, she appears dyspneic in bed at an angle of 45 degrees or less. Her vital signs are as follows: heart rate 124 beats/min, blood pressure 164/98, respiratory rate 28 breaths/min, temperature 37.6°C (99.6°F), and O_2 saturation 89% on room air. There is dullness to percussion and decreased breath sounds over the lower half of the right lung field. Neck veins are elevated. Electrocardiogram shows tachycardia with low voltage. Which of the following is most likely to be seen on imaging?

A. A large apical mass invading the chest wall and brachial plexus
B. An enlarged cardiac silhouette
C. Complete opacification of the right hemithorax
D. Normal chest radiographs
E. Pneumothorax with total collapse of the right lung

II-15. In the patient described above, the initial therapy should include which of the following?

A. Broad-spectrum antibiotics
B. Chemotherapy with erlotinib
C. Emergent radiation therapy
D. IV furosemide to achieve brisk diuresis
E. Pericardiocentesis

II-16. A 58-year-old woman with known stage IV breast cancer presents to the emergency department with inability to move her legs. She has had lower back pain for the past 4 days and has found it difficult to lie down. There is no radiating pain. Earlier today, the patient lost the ability to move either of her legs. In addition, she has been incontinent of urine recently. She was diagnosed previously with metastatic disease to the lung and pleura from her breast cancer but was not known to have spinal or brain metastases. Her physical examination confirms absence of movement in the bilateral lower extremities associated with decreased to absent sensation below the umbilicus. There is increased tone and 3+ deep tendon reflexes in the lower extremities with crossed adduction. Anal sphincter tone is decreased, and the anal wink reflex is absent. What is the most important first step to take in the management of this patient?

A. Administration of IV dexamethasone 10 mg
B. Consult neurosurgery for emergent spinal decompression
C. Consult radiation oncology for emergent spinal radiation
D. Perform MRI of the brain
E. Perform MRI of the entire spinal cord

II-17. A 21-year-old man is treated with induction chemotherapy for acute lymphoblastic leukemia. His initial white blood cell count prior to treatment was 156,000/μL. All of the following are expected complications during his treatment EXCEPT:

A. Acute kidney injury
B. Hypercalcemia
C. Hyperkalemia
D. Hyperphosphatemia
E. Hyperuricemia

II-18. In the patient described in question II-17, all of the following would be important for prevention of the complications described EXCEPT:

A. Administration of allopurinol 300 mg/m^2 daily
B. Administration of IV fluids at a minimum of 3000 mL/m^2 daily
C. Alkalinization of the urine to a pH of greater than 7.0 by administration of sodium bicarbonate
D. Frequent monitoring of serum chemistries every 4 hours
E. Prophylactic hemodialysis prior to initiating chemotherapy

II-19. A 65- year old African American man comes to the clinic with a "spot" on his foot. He noticed it a few months ago and says it has been getting bigger. It is on the bottom of his foot so he is not sure exactly when it first appeared. He denies any other local or systemic symptoms. He takes metformin for diabetes and losartan for hypertension. On physical examination his vital signs are all within normal limits. His foot appears as pictured in Figure II-19. What is the most likely diagnosis?

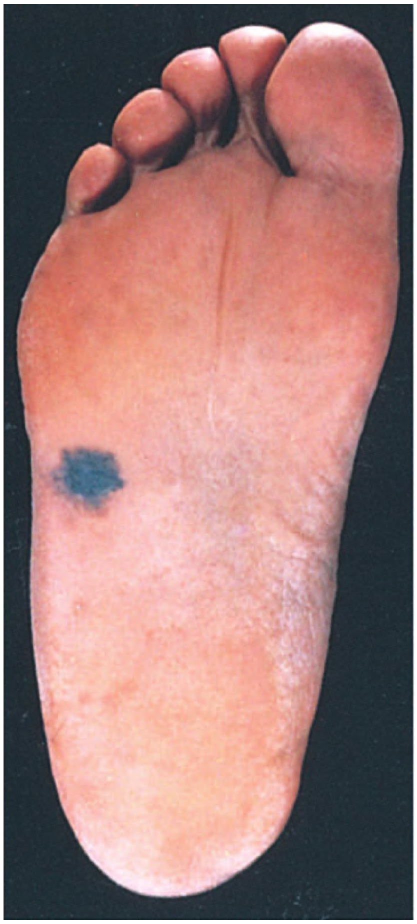


FIGURE II-19

A. Acral lentiginous melanoma
B. Dysplastic nevi
C. Impetigo
D. Lentigo maligna melanoma
E. Syphilis

II-20. A 55-year-old woman presents to her dermatologist with a lesion on her leg that is 8 mm in largest diameter and irregular in shape. She reports this mole has become larger and darker and she wants to have it evaluated. Biopsy confirms melanoma that extends 0.5 mm from the surface and into the dermis with <1 mitosis per millimeter. Which of the following factors has the greatest impact on the patient's prognosis?

A. Anatomic site
B. Breslow thickness
C. Clark level
D. Number of mitoses
E. Sex

II-21. All of the following statements regarding nonmelanoma skin cancer are true EXCEPT:

A. Actinic keratoses and cheilitis are both premalignant forms of squamous cell carcinoma.
B. All forms of ultraviolet light exposure, including tanning beds, increase the risk of nonmelanoma skin cancers.
C. Basal cell carcinoma is most likely to become a metastatic malignancy.
D. Keratoacanthomas that regress spontaneously should be treated as aggressively as other squamous cell cancers as they progress to metastatic disease.
E. Solid organ transplantation is associated with a marked increased risk of both squamous and basal cell carcinoma that can be aggressive and lead to death.

II-22. All of the following have been identified as risk factors for the development of squamous cell carcinoma of the head and neck EXCEPT:

A. Alcohol consumption
B. Epstein-Barr virus infection
C. Human papillomavirus infection
D. Tobacco consumption
E. Treatment of prior head and neck cancer

II-23. A 65-year-old man presented to his primary care doctor initially for enlarged cervical lymph nodes for the past 3 months. He has taken multiple courses of antibiotics without resolution. He smokes one pack of cigarettes daily and also drinks at least a six-pack of beer daily. His physical examination reveals a thin man in no distress. No stridor is heard. The head and neck examination is normal except for 2 submandibular lymph nodes on the left side that are about 2 and 3 cm in size. A fine-needle aspiration of the lymph node demonstrates squamous cell carcinoma. What is the next best step in this patient's management?

A. Ear, nose, and throat (ENT) referral for directed biopsies and staging
B. Continued observation
C. Excisional biopsy of the lymph node
D. Laboratory evaluation of tumor markers
E. Whole-body positron emission tomography scan

II-24. A 60-year-old woman comes to see you in the primary care clinic for a wellness examination. She says she wants to do everything possible to prevent dying of lung cancer since her mother and grandmother died of lung cancer. She has a past medical history only of hypertension. She smoked 2 packs per day of cigarettes for about 20 years but quit 5 years ago. Which of the following would you recommend?

A. Genetic testing given family history
B. Supplementation with beta-carotene supplements
C. Supplementation with vitamin
D. Yearly chest x-rays
E. Yearly low-dose CT scans

II-25. Mr. Blank is a 75-year-old man with a 40 pack-year smoking history. He finally quit last year when he started to develop shortness of breath. His shortness of breath has continued to progress to the point where he is short of breath even at rest. He did not want to go to the doctor, but his daughter finally convinced him to go to the emergency room. There CT imaging revealed a 3-cm left-sided peripheral nodule with three ipsilateral enlarged lymph nodes and a larger left pleural effusion. Lung cancer is suspected, so biopsy of the lung nodule is obtained. What is the next best step in management and why?

A. Await pathology results because if the patient has a *KRAS* mutation, targeted treatments can be offered.
B. Await pathology results because if the patient has an *EGFR* mutation, targeted treatments can be offered.
C. Consult medical oncology for emergent chemotherapy while hospitalized.
D. Consult radiation oncology for emergent radiation therapy while hospitalized.
E. Consult surgical oncology for lobectomy as this is likely the only therapy needed.

II-26. Mr. Takei is a 72-year-old man who presented with a new cough to his primary care physician. Chest imaging revealed a mass in the hilar region of his left lung and a moderate pleural effusion. He underwent thoracentesis and biopsy of the mass, which revealed the presence of hyperchromic, small basophilic atypical cells in the biopsy and the pleural fluid. The cells were also positive for chromogranin and synaptophysin. Which of the following is correct about his disease?

A. MRI of the brain is indicated in all patients.
B. Mr. Takei has disease limited to the thorax and is a candidate for radiation.
C. Surgery alone has a high curative rate for Mr. Takei's stage of disease.
D. Radiation plays no role in therapy for this disease.
E. Few patients are diagnosed with this stage of disease.

II-27. A 64-year-old man seeks evaluation for a solitary pulmonary nodule that was found incidentally. He had presented to the emergency department for shortness of breath and chest pain. A CT pulmonary angiogram did not show any evidence of pulmonary embolism; however, a 9-mm nodule is seen in the periphery of the left lower lobe. No enlarged mediastinal lymph nodes are present. He is a current smoker of 2 packs of cigarettes daily and has done so since the age of 16. He generally reports no functional limitation related to respiratory symptoms. His FEV_1 is 88% predicted, FVC is 92% predicted, and diffusion capacity is 80% predicted. He previously had a normal chest x-ray 3 years ago. What is the next best step in the evaluation and treatment of this patient?

A. Perform a bronchoscopy with biopsy for diagnosis
B. Perform a combined positron emission tomography (PET)/CT to assess for uptake in the nodule and assess for lymph node metastases
C. Perform a follow-up CT scan in 3 months to assess for interval growth
D. Refer the patient to radiation oncology for stereotactic radiation of the dominant nodule
E. Refer the patient to thoracic surgery for video-assisted thoracoscopic biopsy and resection of lung nodule if malignancy is diagnosed

II-28. A 62-year-old man presents to the emergency department complaining of a droopy right eye and blurred vision for the past day. The symptoms started abruptly, and he denies any antecedent illness. For the past 4 months, he has been complaining of increasing pain in his right arm and shoulder. His primary care physician has treated him for shoulder bursitis without relief. His past medical history is significant for chronic obstructive pulmonary disease and hypertension. He smokes one pack of cigarettes daily. He has chronic daily sputum production and stable dyspnea on exertion. On physical examination, he has right eye ptosis with unequal pupils. His pupil is 2 mm on the right and not reactive, whereas the left pupil is 4 mm and reactive. However, his ocular movements appear intact. His lung fields are clear to auscultation. On extremity examination, there is wasting of the intrinsic muscles of the hand. Which of the following would be most likely to explain the patient's constellation of symptoms?

A. Enlarged mediastinal lymph nodes causing occlusion of the superior vena cava
B. Metastases to the midbrain from small-cell lung cancer
C. Paraneoplastic syndrome caused by antibodies to voltage-gated calcium channels
D. Presence of a cervical rib on chest x-ray
E. Right apical pleural thickening with a masslike density measuring 1 cm in thickness

II-29. As an oncologist, you are considering treatment options for your patients with lung cancer, including small-molecule therapy targeting the epidermal growth factor receptor (EGFR). Which of the following patients is most likely to have an *EGFR* mutation?

A. A 23-year-old man with a hamartoma
B. A 33-year-old woman with a carcinoid tumor
C. A 45-year-old woman who has never smoked with an adenocarcinoma
D. A 56-year-old man with a 100 pack-year history of tobacco use with small-cell lung carcinoma
E. A 76-year-old man with squamous cell carcinoma and a history of asbestos exposure

II-30. All of the following factors are associated with an increased risk of breast cancer EXCEPT:

A. Early age at menarche
B. Full-term pregnancy early in life
C. Long duration of breastfeeding
D. Moderate alcohol intake
E. Moderate central obesity

II-31. A 64-year-old woman returns to your clinic after being "lost to follow-up" for 3 years. She reports that she was diagnosed with left-sided, stage I, estrogen/progesterone receptor–positive breast cancer 3 years ago. She was then treated with surgery, radiation, and adjuvant hormonal therapy. She did not receive chemotherapy. She reports that she has been doing well, without any symptoms currently. Her last mammogram was 15 months ago. Her CA 27-29 level was 40 U/mL at the time of diagnosis. Which of the following tests would be recommended for her now?

A. CT chest, abdomen, pelvis
B. Echocardiogram
C. Mammogram
D. Serum chemistry studies
E. Tumor markers (CA 27-29)

II-32. Which of the following history or physical examination findings should prompt investigation for hereditary nonpolyposis colon cancer screening in a 32-year-old man?

A. Father, paternal aunt, and paternal cousin with colon cancer with ages of diagnosis of 54, 68, and 37 years, respectively
B. Innumerable polyps visualized on routine colonoscopy
C. Mucocutaneous pigmentation
D. New diagnosis of ulcer

II-33. A 56-year-old man presents to a physician with weight loss and dysphagia. He feels that food gets stuck in his midchest such that he no longer is able to eat meat. He reports his diet consists primarily of soft foods and liquids. The symptoms have progressively worsened over 6 months. During this time, he has lost about 50 lb. He occasionally gets pain in his midchest that radiates to his back and also occasionally feels that he regurgitates undigested foods. He has no history of gastroesophageal reflux disease. He does not regularly seek medical care. He is known to have hypertension but takes no medications. He drinks 500 mL or more of whiskey daily and also smokes 1.5 packs of cigarettes per day. On physical examination, the patient appears cachectic with temporal wasting. He has a body mass index of 19.4 kg/m^2. His blood pressure is 198/110, heart rate is 110 beats/min, respiratory rate is 18 breaths/min, temperature is 37.4°C (99.2°F), and oxygen saturation is 93% on room air. His pulmonary examination shows decreased breath sounds at the apices with scattered expiratory wheezes. His cardiovascular examination demonstrates an S_4 gallop with a hyperdynamic precordium. A regular tachycardia is present. Blood pressures are equal in both arms. Liver span is not enlarged. There are no palpable abdominal masses. What is the most likely cause of the patient's presentation?

A. Adenocarcinoma of the esophagus
B. Ascending aortic aneurysm
C. Esophageal stricture
D. Gastric cancer
E. Squamous cell carcinoma of the esophagus

II-34. Which of the following risk factors is associated with both adenocarcinoma and squamous cell carcinoma of the esophagus?

A. Barrett esophagus
B. Chronic gastroesophageal reflux disease
C. Cigarette smoking
D. Lye ingestion
E. Male sex

II-35. Which of the following chemopreventive treatments is associated with reduced risk of colon cancer and reduced risk of death from colon cancer?

A. Aspirin
B. Antibiotics
C. Beta-carotene
D. Statins

II-36. Which of the following infectious agents is associated with the development of anal cancer?

A. *Helicobacter pylori*
B. Hepatitis C
C. HIV
D. Human papillomavirus
E. *Streptococcus bovis*

II-37. Which of the following cancers has seen an increase in worldwide incidence and mortality rates?

A. Central nervous system cancers
B. Leukemia
C. Lymphoma
D. Liver cancer
E. Prostate cancer

II-38. A 69-year-old woman presented to the clinic initially with painless jaundice that was noticed by her son when he came to visit for Christmas. CT imaging and subsequent biopsy demonstrate a single lesion that was 2.9 cm in size and biopsy proven to be intrahepatic cholangiocarcinoma. Which of the following treatments has the highest likelihood of survival?

A. Liver transplantation
B. Local regional radiotherapy
C. Surgical resection
D. Systemic chemotherapy

II-39. A 59-year-old man with known cirrhosis due to prior hepatitis C infection is brought to the clinic by his family due to complaints of 1 month of worsening malaise, abdominal bloating, and nausea with 1 week of right upper quadrant pain. His physical examination is notable for normal vital signs (baseline low blood pressure) and new hepatomegaly. Which of the following statements is true regarding the possibility of hepatocellular carcinoma (HCC)?

A. Fluorodeoxyglucose-positron emission tomography scan is more sensitive for showing primary tumor than CT or ultrasound.
B. Hepatomegaly is an uncommon finding in hepatocellular carcinoma.
C. Imaging criteria alone (without biopsy) have a <75% specificity for the diagnosis.
D. Serum α-fetoprotein is the most sensitive test but is not specific.
E. Ultrasound is an excellent screening test for this patient.

II-40. A 38-year-old woman, with a strong family history of cancer, comes to your office after getting the results of genetic testing that she had done after buying a kit on a promotional Christmas sale. She is most worried about her risk of pancreatic cancer because her grandmother died of pancreatic cancer. All of the following genes are associated with an increased risk of pancreatic cancer EXCEPT:

A. *BRCA2*
B. *CFTR*
C. *MLH1*
D. *PALB2*
E. *PMS2*

II-41. A 65-year-old man is evaluated in the clinic for 1 month of progressive painless jaundice and a 10-lb unintentional weight loss. His physical examination is unremarkable. A dual-phase contrast CT shows a suspicious mass in the head of the pancreas with biliary ductal dilation. Which of the following is the best diagnostic test to evaluate for suspected pancreatic cancer?

A. CT-guided percutaneous needle biopsy
B. Endoscopic ultrasound–guided needle biopsy
C. Endoscopic retrograde cholangiopancreatography with pancreatic juice sampling for cytopathology
D. Fluorodeoxyglucose-positron emission tomography imaging
E. Serum CA 19-9

II-42. Ms. Brown is a 59-year-old-woman who presents with new wheezing. She also reports 3 weeks of watery diarrhea, flushing, and abdominal pain. She has no history of asthma or respiratory disease and is a never smoker. Her vital signs are within normal limits at presentation. On chest x-ray there are multiple lung nodules that are concerning for metastatic disease. She undergoes esophagogastroduodenoscopy and colonoscopy and is found to have a lesion in the small intestine that is biopsied and diagnosed as neuroendocrine tumor. Which of the following is true regarding cardiac complications of this disease?

A. Carcinoid heart disease is increasing in frequency and severity.
B. Cardiac manifestations are rare, occurring in <3% of patients over the course of the disease.
C. Cardiac disease is due to the formation of fibrotic plaques involving the endocardium.
D. Left-sided valvular lesions are the most common manifestations.
E. When present, heart failure rarely develops.

II-43. A 68-year-old man comes to his physician complaining of 2 months of increasing right flank pain with 1 month of worsening hematuria. He was treated for cystitis at a walk-in clinic 3 weeks ago with no improvement. He also reports poor appetite and 5-lb weight loss. His physical examination is notable for a palpable mass in the right flank measuring >5 cm. His renal function is normal. All of the following are true about this patient's likely diagnosis EXCEPT:

A. Anemia is more common than erythrocytosis.
B. Hematuria, flank pain, and a palpable mass are the most common presentation.
C. Obesity increased his risk.
D. Patients with von Hippel-Lindau syndrome may present with this malignancy.
E. The most likely pathology is clear cell carcinoma.

II-44. In the patient described in question II-43, imaging shows a 10-cm solid mass in the right kidney and multiple nodules in the lungs consistent with metastatic disease. Needle biopsy of a lung lesion confirms the diagnosis of renal cell carcinoma. All of the following treatments are reasonable to consider for this patient EXCEPT:

A. Cytotoxic chemotherapy
B. Cytokine therapy
C. Nephrectomy
D. Immunotherapy
E. Tyrosine kinase inhibitors

II-45. A 63-year-old man with a history of Cowden syndrome complains of notable pink-tinged urine for the last month. At first he thought it was due to eating beets, but it has not cleared. His medical history is notable for hypertension and cigarette smoking. He does report some worsening urinary frequency and hesitancy over the last 2 years. Physical examination is unremarkable. Urinalysis is notable for gross hematuria with no white cells or casts. Renal function is normal. Which of the following statements regarding this patient is true?

A. Cytology is rarely successful in identifying high-grade bladder cancers.
B. Females are more likely than males to develop bladder cancer.
C. Intravesicular therapy is not an effective strategy for non-muscle invasive bladder cancers.
D. Squamous cell carcinoma is the likely histology found if biopsied.
E. The history of Cowden syndrome puts him at increased risk of developing bladder cancer.

II-46. An 85-year-old man presents because of urinary hesitancy, straining, and a weak stream. This has been going on for approximately the last 20 years but now is getting quite bothersome. On a digital rectal examination he is noted to have an enlarged prostate without any masses. He has a prostatic-specific antigen of 3 ng/mL, which has been stable for the past 10 years. You prescribe tamsulosin for him. What is the proposed mechanism of action that might improve symptoms with this medication?

A. Decreases prostate volume
B. Prolongs the effect of nitrous oxide
C. Reduces parasympathetic tone
D. Reduces sympathetic tone

II-47. All of the following statements regarding prostate cancer prevention are true EXCEPT:

A. Cruciferous vegetables and tomatoes may be protective against prostate cancer.
B. 5α-reductase inhibitors have been shown in randomized controlled trials to reduce the risk of developing prostate cancer.
C. There are no agents currently approved for the prevention of prostate cancer.
D. Vitamin E has been shown in clinical trials to reduce the risk of developing prostate cancer.

II-48. Which of the following statements regarding prostate-specific antigen (PSA) is true?

A. Men with elevated PSAs should be treated with antibiotics, regardless of the presence or absence of symptoms.
B. PSA immunohistochemical staining can be used to establish a prostate cancer diagnosis.
C. PSA is produced exclusively by prostate cancer cells.
D. Serum levels can be increased up to 10-fold after digital rectal examination.
E. The U.S. Preventive Services Task Force recommends PSA screening for men up to age 80.

II-49. A 54-year-old man is evaluated in an executive health program. On physical examination, he is noted to have an enlarged prostate with a right lobe nodule. He does not recall his last digital rectal examination and has never had a prostate-specific antigen (PSA) test. Based on this evaluation, which of the following is recommended next?

A. Bone scan to evaluate for metastasis
B. PSA
C. PSA now and in 3 months to measure PSA velocity
D. Repeat digital rectal examination in 3 months
E. Transrectal ultrasound-guided biopsy

II-50. Which of the following statements regarding the long-term care for patients with advanced testicular germ cell tumors is true?

A. Cisplatin chemotherapy does not contribute to late toxicities.
B. In patients who are treated with etoposide, there is an increased risk of developing acute lymphoid leukemia.
C. Long-term survival is unlikely.
D. There is a decreased risk of secondary malignancies due to chemotherapy.
E. There is an increased risk of cardiovascular disease as a complication of chemotherapy.

II-51. A 26-year-old man presents with pain and swelling of his right testicle that has persisted after an empiric treatment for epididymitis. Ultrasound confirms a 1.5 × 2-cm solid mass, suspicious for testicular cancer. Radical inguinal orchiectomy confirms the mass as a seminoma with disease limited to the testis (tumor stage pT1). Chest, abdomen, and pelvis CT shows no evidence of metastatic disease or lymphadenopathy. Results of serum tumor markers demonstrate the following (normal values in parentheses): α-fetoprotein 5 ng/mL (<10 ng/ mL), β-human chorionic gonadotropin 182 U/L (0.2–0.8 U/L), and lactate dehydrogenase 432 U/L (100–190 U/L). Following resection, all tumor markers became undetectable after an appropriate interval. Which is the next best step in this patient's treatment?

A. Immediate retroperitoneal radiation therapy
B. Nerve-sparing retroperitoneal lymph node dissection
C. Single-dose therapy with cisplatin
D. Surveillance alone with treatment only if relapse detected
E. Either A or D, because both are associated with a near 100% cure rate

II-52. Which of the following statements describes the relationship between testicular tumors and serum markers?

A. β-human chorionic gonadotropin (β-hCG) and α-fetoprotein (AFP) should be measured when following the progress of a tumor.
B. β-hCG is limited in its usefulness as a marker because it is identical to human luteinizing hormone.
C. Measurement of tumor markers the day after surgery for localized disease is useful in determining completeness of the resection.
D. More than 40% of nonseminomatous germ cell tumors produce no cell markers.
E. Pure seminomas produce AFP or β-hCG in more than 90% of cases.

II-53. A 42-year-old woman seeks evaluation for >6 months of postcoital bleeding without dyspareunia. She also notes some recent spotting between her regular menses. She has no past medical history other than an intrauterine device placed approximately 10 years ago, has multiple sexual partners, and works as an accountant. She has not sought gynecologic evaluation for 10 years. Pelvic examination reveals an abnormal appearance of the cervix with an abnormal Pap smear, positive human papillomavirus (HPV) test, and negative for HIV, chlamydia, gonorrhea, and syphilis studies. A cervical biopsy shows squamous cell carcinoma confined to the cervix. All of the following statements regarding this woman's condition are true EXCEPT:

A. Cervical cancer is an uncommon cancer worldwide.
B. Her cancer is related to HPV infection.
C. HPV vaccination before initiation of sexual activity can decrease the risk of developing an abnormal Pap smear.
D. She has stage I cervical cancer.
E. With surgical therapy, her 5-year survival is >80%.

II-54. Which of the following is rarely associated with an increased risk of developing a sarcoma?

A. Human herpes virus 8
B. HIV
C. Li-Fraumeni syndrome
D. Prior radiation therapy
E. Trauma or previous injury

II-55. A 55-year-old woman presents to the emergency department after a minor motorcycle collision complaining of diffuse chest pain. Her chest radiograph shows multiple 2- to 4-cm lung nodules and masses without cavitation in all lobes. Her physical examination is totally normal other than some diffuse chest pain from the accident. She has no past medical history and takes no medications, other than a multivitamin. She exercises regularly and had a negative colonoscopy and mammogram within the last 2 years. She works as a librarian and rides motorcycles for recreation. There is no history of cigarette or illicit drug use. Abdominal, pelvic, and head imaging shows no likely primary lesions. A bronchoscopic biopsy of a lung lesion is performed and shows histology consistent with moderately well-differentiated adenocarcinoma. There were no airway abnormalities. Her fluorodeoxyglucose-positron emission tomography (FDG-PET) scan shows no lesions other than those in the lung, and repeat colonoscopy and mammography are normal. All of the following statements regarding her carcinoma are true EXCEPT:

A. Cancer of unknown primary (CUP) accounts for <1% of all cancers.
B. Tumor markers, when elevated, are rarely helpful in determining the site of origin.
C. Most cancers of unknown primary are adenocarcinoma.
D. The current diagnostic yield with imaging and immunochemistry is ~20–30% for CUP patients.
E. Most CUP patients harbor a clinically relevant genomic alteration by next-generation sequencing.

II-56. Mr. Byron is a 72-year-old man with an 80 pack-year smoking history who presents to your clinic for his annual physical. He has a history of hypertension and hyperlipidemia that has been well controlled on losartan and atorvastatin. He used to work in the steel mills but finally retired this past year. He notes a new cough that has been going on for the past 3 months as well as a 30-lb weight loss since his last visit. He denies any fevers, night sweats, or chills. His vital signs are normal. In routine labs you note that he has a new increase in mature granulocytes but no other laboratory abnormalities. Which of the following statements regarding his elevated white blood cell count is true?

A. Approximately 70% of patients with solid tumors have granulocytosis.
B. The granulocytosis is likely the cause of his symptoms.
C. Treatment targeting the granulocytosis should begin immediately.
D. Thirty-five percent of patients with granulocytosis have an underlying cancer.
E. Some tumors have been documented to produce granulocyte colony-stimulating factor, which may be contributing to the granulocytosis found in this patient.

II-57. A 22-year-old comes to you to establish care. He just graduated from college and moved to your state to begin a job in the tech industry. He is living with his college girlfriend who he intends to marry and start a family with in the next few years. He is well versed in the health care system because he is a survivor of childhood leukemia and had a bone marrow transplant from his brother that was curative. He has had no signs of malignancy for the past 10 years. All of the following statements regarding his cancer and cancer treatment are true, EXCEPT:

A. Age at time of treatment is not related to fertility outcomes in childhood survivors of cancer.
B. Follow-up for his cancer and related toxicities should continue indefinitely.
C. Intrathecal methotrexate may contribute to neurocognitive dysfunction in survivors of acute lymphoblastic leukemia treatment.
D. Suicidal ideation and suicide have an increased prevalence in cancer patients and survivors.
E. Testicles and ovaries in prepubertal patients are less sensitive to radiation damage.

II-58. A 29-year-old man presents to your clinic with worsening fatigue. He has no significant past medical history. He works in a gym, participates in fitness competitions, and follows a very strict vegetarian diet. You check routine labs, which are normal except for his complete blood count, which shows a hemoglobin of 10.2 g/dL, mean corpuscular volume of 74 fL, serum iron of 29 μg/dL, serum ferritin of 14 μg/L, total iron-binding capacity of 410 μg/dL, and percent saturation of 10%. His complete blood count was normal 3 years ago when it was last checked. Which of the following would be the best treatment for this patient?

A. Desferrioxamine
B. Folic acid supplementation
C. Iron supplementation
D. Treatment of an underlying inflammatory disease
E. Vitamin B_{12} supplementation

II-59. Which of the following proteins is most responsible for iron transport in the plasma?

A. Albumin
B. Ferritin
C. Haptoglobin
D. Hemoglobin
E. Transferrin

II-60. A 13-year-old boy comes into the hospital with severe pain in his bilateral hips, arms, and diffuse body aches. He has had similar episodes but has not required hospitalization. He is not on any medications. He plays soccer part of the year but has not been playing recently and has not had any trauma. On initial labs, his comprehensive metabolic panel is normal except for a total bilirubin of 1.5 mg/dL. Complete blood count is notable for microcytic anemia. His peripheral smear is shown in Figure II-60.

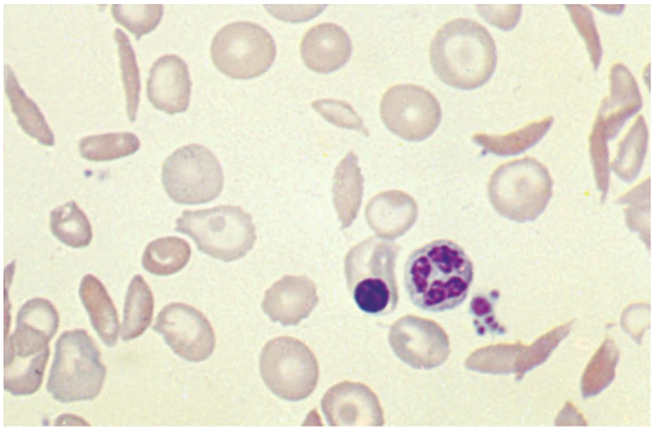


FIGURE II-60

Which of the following is the most likely mechanism of this diagnosis?

A. A somatic mutation that causes deranged messenger RNA splicing of the globin gene.
B. Elevated carbon monoxide levels.
C. Mutation in the β-globin gene that changes the sixth amino acid from glutamic acid to valine.
D. One of the four α-globin loci is deleted.

II-61. A 22-year-old man with known sickle cell anemia is admitted to the intensive care unit with diffuse body pain, shortness of breath, fever, and cough. He started having a bone pain crisis 1 day ago and tried to treat it at home with oral hydration. On examination, his blood pressure and heart rate are elevated, and he is in obvious pain and respiratory discomfort. His room air SaO_2 is 83% and increases to 91% on a nonrebreather oxygen face mask. His chest radiograph shows bilateral diffuse alveolar infiltrates. This is his third similar episode in the last 12 months. All of the statements regarding his condition are true EXCEPT:

A. Chronic therapy with oral hydroxyurea should be considered.
B. He is having sickle cell acute chest syndrome.
C. He should receive daily sildenafil.
D. Hematocrit should be maintained

II-62. A 28-year-old woman is referred to your clinic for evaluation of anemia that was found on a life insurance screening examination. She reports being healthy, takes no medications other than a multivitamin with iron, and only admits some recent fatigue on exertion in the past 6–9 months. She menstruates regularly with 3- to 4-day menses that have not changed in years. She eats a normal omnivorous diet, smokes one pack of cigarettes per day, and does not use illicit drugs. The results of her complete blood count reveal a white blood cell count of 4.0/μL, platelet count of 235,000/μL, and hemoglobin of 8 g/dL with a mean corpuscular volume of 105. Her blood smear is shown in Figure II-62. She has normal renal

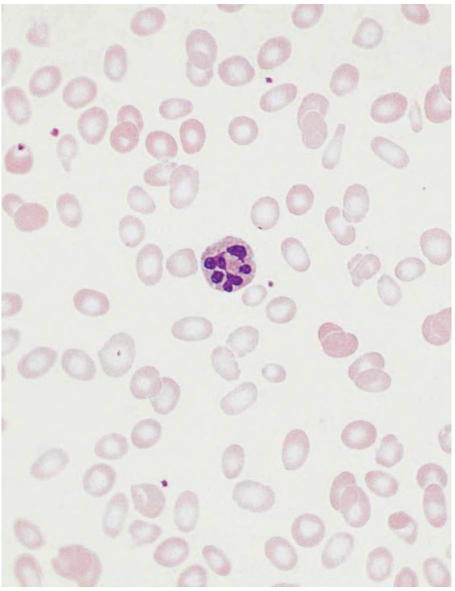


FIGURE II-62 Reproduced with permission from Hoffbrand AV et al: *Postgraduate Haematology*, 5th ed. Oxford: Blackwell Publishing, 2005.

and liver function. Which of the following is the most likely diagnosis?

A. Acute myeloblastic anemia
B. Hereditary spherocytosis
C. Iron-deficiency anemia
D. Nutritional megaloblastic anemia
E. Pernicious anemia

II-63. In the patient described in question II- 62, which of the following is the next best study to confirm the diagnosis?

A. Bone marrow biopsy
B. Hemoglobin electrophoresis
C. Serum homocysteine level
D. Serum iron and transferrin levels
E. Serum vitamin B_{12} level

II-64. A 47-year-old woman comes to your office for a sick visit. This morning she reports passing blood instead of urine. On review of symptoms, she denies any other symptoms except for occasional recurrent attacks of severe abdominal pain for which she has had other urgent care visits but no etiology was found. She has no other past medical history, takes no medications other than a multivitamin, and has no family history of malignancy. Given the bleeding, you repeat a complete blood count. The results are below:

White blood cell count 2.9 × 10^9/L
Hemoglobin 10.2 g/dL (mean corpuscular volume 82 fL)
Platelet count 119 × 10^9/L

Her complete blood count 1 year ago was normal. Her chemistries are only notable for an elevated unconjugated bilirubin and a markedly elevated lactate hydrogenase. Which of the following diagnostic test results would you expect to find in this patient?

A. Blood cultures
B. Flow cytometry with a discrete population that is CD59 and CD55 negative
C. Mutation in the gene for glucose-6-phosphate dehydrogenase gene
D. Presence of the Donath-Landsteiner antibody
E. Spherocytes on peripheral blood smear with failed osmotic fragility test

II-65. A 24-year-old man returns to the acute care clinic complaining of 1 day of worsening malaise, weakness, abdominal pain, and discolored dark urine. He was at the clinic yesterday where he was diagnosed with a possible staphylococcal skin carbuncle and treated with empiric trimethoprim/sulfamethoxazole. His physical examination is notable for mild jaundice, normal vital signs, and no focal findings other than the carbuncle in his left axilla. His complete blood count shows that his hemoglobin has fallen from 13 to 8 g/dL and his bilirubin has gone from normal to 3.0 mg/dL. His urine dipstick is positive for bilirubin. A peripheral blood smear is obtained that demonstrates an abnormality (Figure II-65, arrow). Which of the following is the most likely cause of his new anemia?

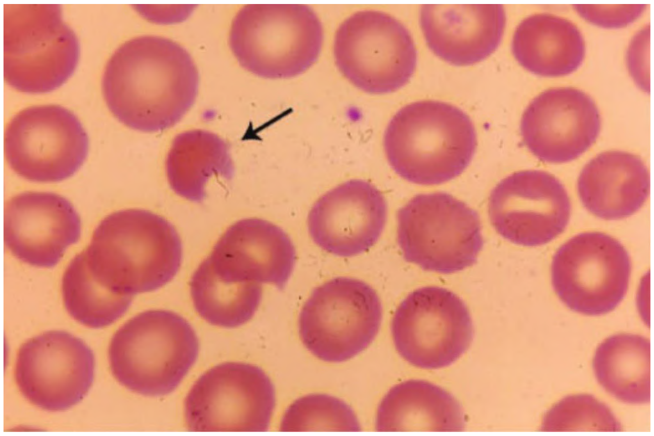


FIGURE II-65 Reproduced with permission from Lichtman MA et al: *Lichtman's Atlas of Hematology 2016*. New York: McGraw Hill, 2017.

A. Glucose 6-phosphate dehydrogenase deficiency
B. Hemolytic-uremic syndrome
C. Hereditary spherocytosis
D. Iron-deficiency anemia
E. Thrombotic thrombocytopenic purpura

II-66. You are seeing Ms. Stoked, who is a 19-year-old collegiate rower who has been in excellent health and takes no chronic medications, for new-onset severe fatigue and left upper abdominal pain. She was treated 2 days ago in the health center for presumed gonorrhea with ceftriaxone and azithromycin. Her past medical history is only notable for one prior episode of presumed gonorrhea when she was 17 years old. Her physical examination is notable for a heart rate of 100 beats/min and a palpable spleen. Stool is negative for heme. Laboratory examination is notable for a hemoglobin of 5 g/dL with normal white blood cells and platelets. Peripheral blood smear shows an excess of spherocytes. Which of the following tests will most likely confirm the diagnosis?

A. ADAMTS-13 activity assay
B. Direct antiglobulin (Coombs) test
C. Flow cytometry
D. G6PD deficiency assay
E. Hemoglobin electrophoresis

II-67. A 68-year-old woman comes to the clinic with fatigue, intermittent fevers, and night sweats for the past 2 weeks. She denies any recent travel or sick contacts. Her physical examination reveals pale conjunctiva but is otherwise normal. Her vital signs are notable only for a temperature of 38.0°C (100.4°F). The metabolic panel is normal, but her complete blood count reveals a white blood cell count of 900/μL, hemoglobin of 8.0g/dL, and a platelet count of 98,000/ μL. Which of the following is the least likely cause of her current symptoms?

A. Acquired aplastic anemia
B. Copper deficiency
C. Myelodysplastic syndrome
D. Myelofibrosis
E. Parvovirus infection

II-68. A 73-year-old man comes to the primary care clinic complaining of 4–6 weeks of increasing malaise, fatigue, dyspnea on exertion, and occasional night sweats. His past medical history is notable for hypertension and hyperlipidemia. Medications include lisinopril and atorvastatin. He had a screening colonoscopy 6 months ago at which time his laboratory studies were normal. His physical examination today is only notable for a heart rate of 105 beats/min and pale mucous membranes. Lungs are clear, and there are no new cardiac findings. Electrocardiogram shows sinus tachycardia but no acute changes. Laboratory studies show normal electrolytes, but his white blood cell count is 1300/μL, platelet count is 35,000/μL, and hemoglobin is 7.5 g/dL. Examination of his peripheral smear confirms the pancytopenia and notes the red blood cells are macrocytic, and there are 3% blasts present. All of the following statements regarding his condition are true EXCEPT:

A. Azacitidine may improve his blood counts and prolong survival.
B. Children with Down syndrome are also at risk.
C. He is at high risk of developing acute myeloid leukemia.
D. Hematopoietic stem cell transplantation is contraindicated.
E. Increasing percentages of bone marrow blasts correlate with worsening prognosis.

II-69. On yearly labs done to follow a 40-year-old patient with a history of iron-deficiency anemia, you notice the development of new thrombocytosis with a platelet count of 750 × 10^9/L. All of the following statements regarding thrombocytosis are true EXCEPT:

A. Iron-deficiency anemia can cause thrombocytosis.
B. Patients with essential thrombosis have a similar survival compared with the general population.
C. The incidence of thrombosis in this patient is no higher than age-matched controls.
D. This could be essential thrombosis, which is a clonal hematopoietic stem cell disorder with a female predominance.
E. Treatment with aspirin should be started immediately.

II-70. A 53-year-old man is sent to you for evaluation of an elevated hematocrit found incidentally on lab testing. He was removing drywall in a house and cut his upper arm. A complete blood count before his arm was stitched revealed a hematocrit of 59% with hemoglobin of 20 g/dL, white blood cell count of 15.4/μL with a normal differential, and platelet count of 445,000/ μL. His physical examination is notable for a room air oxygen saturation of 95%, blood pressure of 145/85, and a palpable spleen. He has no past medical history, is a nonsmoker, drinks rarely on social occasions, and is taking no medications. The patient reports his last contact with a physician was 2–3 years ago, and he recalls no abnormalities reported on blood testing. Which of the following is the next diagnostic step?

A. Arterial blood gas
B. Erythropoietin level
C. Red blood cell mass
D. Pulmonary function tests
E. Renal ultrasound

II-71. In the patient described in question II-70, if secondary causes of elevated hemoglobin are ruled out, which of the following is the recommended therapy?

A. Aspirin
B. Hydroxyurea
C. Imatinib
D. Phlebotomy to maintain hemoglobin <14 g/dL
E. Warfarin

II-72. A 78-year-old-man comes to the clinic reporting dramatically increasing fatigue over the past month. He has had two visits to urgent care over the same time course because of sinus infections and was treated first with azithromycin and then with amoxicillin. He completed his course of amoxicillin 3 days ago but continues to feel unwell. He is no longer febrile, but he does complain of continued headache. He has no significant past medical history and other than the antibiotics, has not been taking any other medications. On examination, his vital signs are within normal limits. He has pale conjunctiva and scattered mucosal petechiae with some mild sinus tenderness. Cardiac, pulmonary, and neurologic exams are normal. Abnormal values from his comprehensive metabolic panel and complete blood count are shown below:

Sodium (Na): 140 mEq/L
Potassium (K): 5.0 mEq/L
Creatinine (Cr): 1.5
White blood cell count: 14,000/L
Hemoglobin: 9.2g/dL
Platelets: 11 × 10^9/L

His peripheral blood smear is shown in Figure II-72.

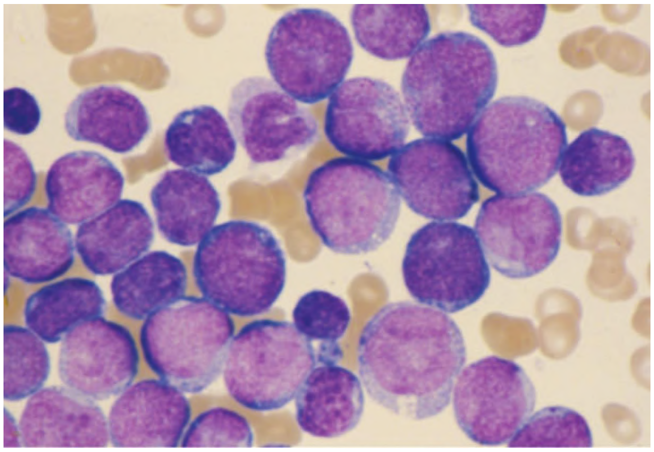


FIGURE II-72

Which of the following molecular markers is associated with a poor prognosis in this disease?

A. T(8;21)
B. Inv(16)
C. No cytogenetic abnormalities
D. NPM1
E. Monosomy karyotype

II-73. A 64-year-old man presents with 3 weeks of increasing fatigue and bleeding while brushing his teeth. Physical examination is notable for low-grade fever and normal heart rate, blood pressure, and respiratory rate. He has splenomegaly. A complete blood count shows marked pancytopenia with blasts present on peripheral smear. A bone marrow aspirate and biopsy result in the diagnosis of acute promyelocytic leukemia with the t(15;17)(q22;q12) cytogenetic rearrangement. Which of the following medications that is specific to acute promyelocytic leukemia will be included in his induction chemotherapy?

A. Acyclovir
B. Daunorubicin
C. Rituximab
D. Sildenafil
E. Tretinoin

II-74. All of the following statements regarding chronic myeloid leukemia (CML) are true EXCEPT:

A. Allogeneic stem cell transplant is usually offered as second- or third-line therapy.
B. Family history and prior alkylating chemotherapy are associated with an increased risk of developing CML.
C. Most patients present in chronic phase, rather than accelerated or blastic phase, CML.
D. The disease is driven by the *BCR-ABL1* chimeric gene product.
E. The estimated 10-year survival rate with current treatments is 85%.

II-75. Which of the following statements regarding acute lymphoblastic lymphoma (ALL) is true?

A. BCR-ABL1 of Ph-like ALL has increasing frequency with age.
B. Patients with Down syndrome are at increased risk of developing acute myelogenous leukemia (AML) but not ALL.
C. Lumbar puncture is an essential diagnostic measure.
D. Most adult ALLs are of T-cell origin.
E. There are no infectious agents associated with the disease.

II-76. A 73-year-old-man comes in for follow-up after a recent hospitalization for a car accident in which he was rear-ended. He suffered no injuries and was released from the emergency room after a full examination and monitoring. On labs done in the emergency room, he was noted to have an elevated white blood cell count to 95 × 10^9/L, predominantly lymphocytes. You do a peripheral smear, which is shown in Figure II-76.

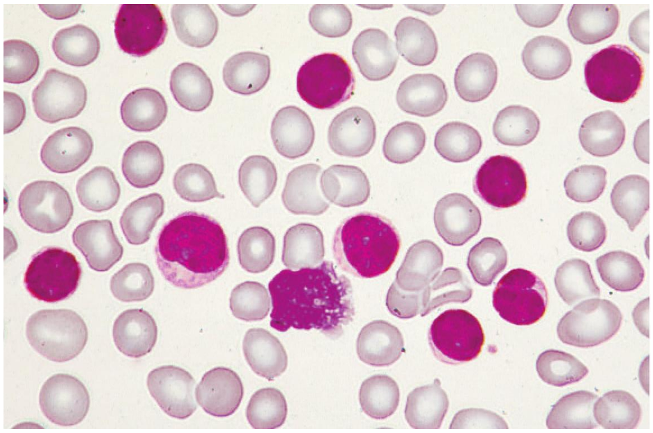


FIGURE II-76 Reproduced with permission from Lichtman M et al: *Williams Hematology*, 7th ed. New York: McGraw-Hill, 2005.

Which of the following is the best next step of action?

A. Admission to the hospital for high-dose induction chemotherapy
B. Bone marrow biopsy
C. Flow cytometry
D. Observation
E. Positron emission tomography-CT scan

II-77. A 29-year-old woman comes to your office because of palpable, nontender cervical lymphadenopathy that has not resolved after 1 month. She has intermittent night sweats but otherwise denies any symptoms. She has no history of any other medical conditions. Physical examination is within normal limits. Complete blood count and comprehensive metabolic panel are within normal limits. A CT scan demonstrates pathologically enlarged lymph nodes in the neck, axilla, and mediastinum. A subsequent positron emission tomography-CT demonstrates that these are fluorodeoxyglucose-avid. Figure II-77 is the representative portion of the excisional biopsy showing large cells with a bilobed nucleus and prominent nucleoli surrounded by a pleomorphic cellular infiltrate.

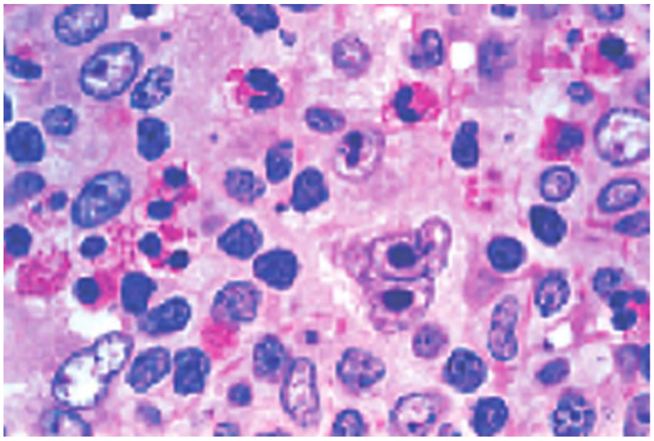


FIGURE II-77

Which of the following statements regarding this patient's diagnosis is true?

A. HTLV-1 is associated with the development of this disease.
B. The existence of the t(14;18) mutation and abnormal expression of BCL-2 protein are confirmatory.
C. The majority of patients will not be cured with chemotherapy alone.
D. The PD-L1 protein is often overexpressed and may contribute to immune evasion.
E. This disease is of T-cell origin.

II-78. You perform a bone marrow biopsy on a patient because of new pancytopenia, the etiology of which has not yet been definitively diagnosed based on laboratory and imaging studies. Unfortunately, you got a "dry tap" with which you were unable to aspirate any bone marrow. Which of the following is the least likely cause of this?

A. Chronic myeloid leukemia
B. Hairy cell leukemia
C. Metastatic carcinoma infiltration
D. Myelofibrosis
E. Normal marrow

II-79. All of the following statements are true regarding the criteria to diagnose the hypereosinophilic syndrome EXCEPT:

A. Increased bone marrow eosinophils must be demonstrated.
B. It is not necessary to have increased circulating eosinophils.
C. Primary myeloid leukemia must be excluded.
D. Reactive eosinophilia (e.g., parasitic infection, allergy, collagen vascular disease) must be excluded.
E. There must be <20% myeloblasts in blood or bone marrow.

II-80. You are seeing a 72-year-old man for follow-up. On routine blood testing last week, you noted an elevated gamma gap. His physical examination is within normal limits. His creatinine was 1.1 mg/dL, albumin 3.9 g/dL, and serum calcium 10.1 mg/dL. A bone marrow biopsy demonstrated 20% clonal plasma cells and serum monoclonal IgA was 15g/L. He is asymptomatic and continues to work as a yoga instructor at a senior center four times per week. Which of the following is the next best step in management?

A. Dexamethasone
B. Lenalidomide plus dexamethasone
C. Positron emission tomography-CT scan
D. Yearly labs and follow-up

II-81. A 58-year-old man is evaluated for sudden-onset cough with yellow sputum production and dyspnea in the emergency department. Aside from systemic hypertension, he is otherwise healthy. His only medication is amlodipine. Chest radiograph shows a right upper lobe alveolar infiltrate, and labs are notable for a blood urea nitrogen of 53 mg/ dL, creatinine of 2.8 mg/dL, calcium of 12.3 mg/dL, total protein of 9 g/dL, and albumin of 3.1 g/dL. Sputum culture grows *Streptococcus pneumoniae*. Which of the following tests will confirm the underlying condition predisposing him to pneumococcal pneumonia?

A. Bone marrow biopsy
B. CT of chest, abdomen, and pelvis with contrast
C. HIV antibody
D. Sweat chloride testing
E. Videoscopic swallow study

II-82. A 64-year-old African American male is evaluated in the hospital for congestive heart failure, renal failure, and polyneuropathy. Physical examination on admission was notable for these findings and raised waxy papules in the axilla and inguinal region. Admission laboratories showed a blood urea nitrogen of 90 mg/dL and a creatinine of 6.3 mg/dL. Total protein was 9.0 g/dL with an albumin of 3.2 g/dL. Hematocrit was 24%, and white blood cell and platelet counts were normal. Urinalysis was remarkable for 3+ proteinuria but no cellular casts. Further evaluation included an echocardiogram with a thickened left ventricle and preserved systolic function. Which of the following tests is most likely to diagnose the underlying condition?

A. Bone marrow biopsy
B. Electromyogram with nerve conduction studies
C. Fat-pad biopsy
D. Right heart catheterization
E. Renal ultrasound

II-83. You are caring for a 65-year-old African American man who was recently told by a cardiologist that he likely has heart failure due to familial amyloidosis based on echocardiography. He has a strong family history of non-systolic heart failure (HFpEF) including his father and a brother who both died in their 60s. Which of the following statements regarding this patient's condition is true?

A. Bone marrow transplantation is curative.
B. Heart failure with diminished systolic function is more typical than heart failure with preserved systolic function.
C. The most common form involves a mutation in the transthyretin gene.
D. This disorder is more common in Hispanic Americans than African Americans.
E. Without intervention, the median survival is <2 years.

II-84. A 56-year-old woman undergoes a haplo-identical bone marrow transplant from her 20-year-old daughter to treat poor risk acute myeloid leukemia. Flu season is approaching and she is curious to know about her risk of infection. Which of the following infections is an acute (likely to happen within the first 30 days) complication of bone marrow transplantation?

A. *Aspergillus*
B. *Candida*
C. Cytomegalovirus
D. Encapsulated bacteria
E. Varicella-zoster

II-85. A 75-year-old man is hospitalized for treatment of a deep venous thrombosis. He had recently been discharged from the hospital about 2 months ago. At that time, he had been treated for community-acquired pneumonia complicated by acute respiratory failure requiring mechanical ventilation. He was hospitalized for 21 days at that time and was discharged from a rehabilitation facility 2 weeks ago. On the day prior to admission, he developed painful swelling of his left lower extremity. A lower extremity Doppler ultrasound confirmed an occlusive thrombus of his deep femoral vein. After an initial bolus, he is started on a continuous infusion of unfractionated heparin at 1600 U/h as he has end-stage renal disease on hemodialysis. His activated partial thromboplastin time (aPTT) is maintained in the therapeutic range. On day 5, it is noted that his platelets have fallen from 150,000/μL to 88,000/μL. All of the following are true regarding his condition EXCEPT:

A. Despite the thrombocytopenia, this condition is associated with thrombosis; not bleeding.
B. It is unlikely to be drug-induced thrombocytopenia as that typically is associated with more severe thrombocytopenia.
C. Laboratory testing can be helpful; however, the diagnosis is a clinical one.
D. Platelets, monocytes, and endothelial cells are activated.
E. Timing of development of this condition is approximately 5–14 days after exposure.

II-86. When heparin-induced thrombocytopenia (HIT) is suspected, one should not delay treatment for laboratory testing as no currently available test has adequate sensitivity or specificity for the diagnosis. The anti-heparin/PF4 antibody test is positive in many individuals who have been exposed to heparin regardless of whether HIT is present. The platelet activation assay is more specific but less sensitive for HIT. HIT remains a clinical diagnosis.

Regarding this patient, which of the following is the most appropriate action?

A. Continue heparin infusion at the current dose and assess for anti-heparin/platelet factor 4 antibodies.
B. Stop all anticoagulation while awaiting results of anti-heparin/platelet factor 4 antibodies.
C. Stop heparin infusion and initiate argatroban.
D. Stop heparin infusion and initiate enoxaparin.
E. Stop heparin infusion and initiate lepirudin.

II-87. A 54-year-old woman presents acutely with alterations in mental status and fever. She was well until 4 days previously when she began to develop complaints of myalgia and fever. Her symptoms progressed rapidly, and today her husband noted her to be lethargic and unresponsive when he awakened. She has recently felt well otherwise. Her only current medication is atenolol 25 mg daily for hypertension. On physical examination, she is responsive only to sternal rub and does not vocalize. Her vital signs are as follows: blood pressure 165/92, heart rate 114 beats/min, temperature 38.7°C (101.7°F), respiratory rate 26 breaths/min, and oxygen saturation 92% on room air. Her cardiac examination shows a regular tachycardia. Her lungs have bibasilar crackles. The abdominal examination is unremarkable. No hepatosplenomegaly is present. There are petechiae on the lower extremities. Her complete blood count shows a hemoglobin of 8.8 g/dL, hematocrit of 26.4%, white blood cell count of 10.2/µL (89% polymorphonuclear cells, 10% lymphocytes, and 1% monocytes), and a platelet count of 54,000/µL. A peripheral blood smear is shown in Figure II-87. Her basic metabolic panel shows a sodium of 137 mEq/L, potassium of 5.4 mEq/L, chloride of 98 mEq/L, bicarbonate of 18 mEq/L, blood urea nitrogen of 89 mg/dL, and creatinine of 2.9 mg/dL. Which of the following most correctly describes the pathogenesis of the patient's condition?

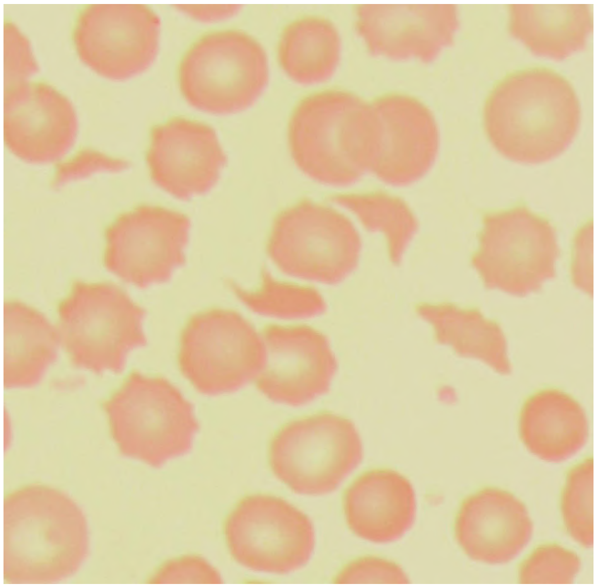


FIGURE II-87

A. Development of autoantibodies to a metalloproteinase that cleaves von Willebrand factor
B. Development of autoantibodies to the heparin/platelet factor 4 complex
C. Direct endothelial toxicity initiated by an infectious agent
D. Inherited disorder of platelet granule formation E, the inherited disorder of von Willebrand factor that precludes binding with factor VIII

II-88. Which of the following is the best initial treatment for the patient described in question II-87?

A. Acyclovir 10 mg/kg IV every 8 hours
B. Ceftriaxone 2 g IV daily plus vancomycin 1 g IV twice daily
C. Hemodialysis
D. Methylprednisolone 1 g IV
E. Plasma exchange

II-89. Factor VII deficiency should be considered with which of the following coagulation abnormalities?

A. Isolated abnormal prothrombin time (PT)
B. Isolated activated partial thromboplastin time (aPTT)
C. Prolongation of both PT and aPTT
D. Normal PT and aPTT with abnormal thrombin time
E. All coagulation tests will be normal

II-90. All of the following genetic mutations are associated with an increased risk of deep venous thrombosis EXCEPT:

A. Factor V Leiden mutation
B. Glycoprotein 1b platelet receptor
C. Heterozygous protein C deficiency
D. Prothrombin 20210G
E. Tissue plasminogen activator

II-91. A 76-year-old man presents to an urgent care clinic with pain in his left leg for 4 days. He also describes swelling in his left ankle, which has made it difficult for him to ambulate. He is an active smoker and has a medical history remarkable for gastroesophageal reflux disease, prior deep venous thrombosis (DVT) 9 months ago that resolved, and well-controlled hypertension. Physical examination is revealing for 2+ edema in his left ankle. A D-dimer is ordered and is elevated. Which of the following makes D-dimer less predictive of DVT in this patient?

A. Age >70 years
B. History of active tobacco use
C. Lack of suggestive clinical symptoms
D. Negative Homan sign on examination
E. Previous DVT in the past year

II-92 to II-95. Match the drug with the target:

II-92. Abciximab	A. Antithrombin
II-93. Apixaban	B. Factor Xa
II-94. Dabigatran	C. Glycoprotein IIb/IIIa
II-95. Enoxaparin	D. Thrombin

ANSWERS

II-1. **The answer is A.** *(Chaps. 65, 66, and 67)* The most significant risk factor for cancer overall is age; two-thirds of all cases were in those aged >65 years. Only a small fraction of cancers occurs in patients with a genetic predisposition. Risk of certain cancers appears to increase modestly (relative risks generally in the 1.0–2.0 range) as body mass index (BMI) increases beyond 25 kg/m^2. A cohort study of >5 million adults included in the UK. Clinical Practice Research Datalink (a primary care database) found that each 5 kg/m^2 increase in BMI was linearly associated with leukemia and cancers of the uterus, gallbladder, kidney, cervix, and thyroid. Positive associations were also noted between BMI and colon, liver, ovarian, and postmenopausal breast cancers, but these associations were not linear and the effect varied by individual characteristics. However, obesity is not the most significant risk factor and high BMI appears to have an inverse association with prostate and premenopausal breast cancer. Tobacco smoking is a strong, modifiable risk factor for cardiovascular disease, pulmonary disease, and cancer. Smokers have an approximately one in three lifetime risk of dying prematurely from a tobacco-related cancer or cardiovascular or pulmonary disease.

II-2. **The answer is E.** *(Chap. 65)* Tumor markers may be useful in patient management in certain tumors. Response to therapy may be difficult to gauge with certainty. However, some tumors produce or elicit the production of markers that can be measured in the serum or urine, and in a particular patient, rising and falling levels of the marker are usually associated with increasing or decreasing tumor burden, respectively. Some clinically useful tumor markers are shown in Table II-2. Tumor markers are not in themselves specific enough to permit a diagnosis of malignancy to be made, but once a malignancy has been diagnosed and shown to be associated with elevated levels of a tumor marker, the marker can be used to assess response to treatment. Monoclonal immunoglobulin would be the best tumor marker to assess for response in this patient with multiple myeloma. The complete blood count and its components are not used as tumor markers; neither is lactate dehydrogenase for multiple myeloma. Positron emission tomography-CT is not used in the follow-up of multiple myeloma. Flow cytometry is useful for some hematologic malignancies; however, multiple myeloma is not one of them.

TABLE II-2 Tumor Markers

Tumor Markers	Cancer	Nonneoplastic Conditions
Hormones		
Human chorionic gonadotropin	Gestational trophoblastic disease, gonadal germ cell tumor	Pregnancy
Calcitonin	Medullary cancer of the thyroid	
Catecholamines	Pheochromocytoma	
Oncofetal Antigens		
α-Fetoprotein	Hepatocellular carcinoma, gonadal germ cell tumor	Cirrhosis, hepatitis
Carcinoembryonic antigen	Adenocarcinomas of the colon, pancreas, lung, breast, ovary	Pancreatitis, hepatitis, inflammatory bowel disease, smoking
Enzymes		
Prostatic acid phosphatase	Prostate cancer	Prostatitis, prostatic hypertrophy
Neuron-specific enolase	Small-cell cancer of the lung, neuroblastoma	
Lactate dehydrogenase	Lymphoma, Ewing sarcoma	Hepatitis, hemolytic anemia, many others
Tumor-Associated Proteins		
Prostate-specific antigen	Prostate cancer	Prostatitis, prostatic hypertrophy
Monoclonal immunoglobulin	Myeloma	Infection, MGUS
CA-125	Ovarian cancer, some lymphomas	Menstruation, peritonitis, pregnancy
CA 19-9	Colon, pancreatic, breast cancer	Pancreatitis, ulcerative colitis
CD30	Hodgkin disease, anaplastic large-cell lymphoma	—
CD25	Hairy cell leukemia, adult T-cell leukemia/lymphoma	—

Abbreviation: MGUS, monoclonal gammopathy of uncertain significance.

II-3. **The answer is B.** *(Chap. 65)* Uterine cancer in women and liver cancer in men and women have been increasing over the past decade (Figure II-3). All other listed cancer types have seen a decline in mortality rates.

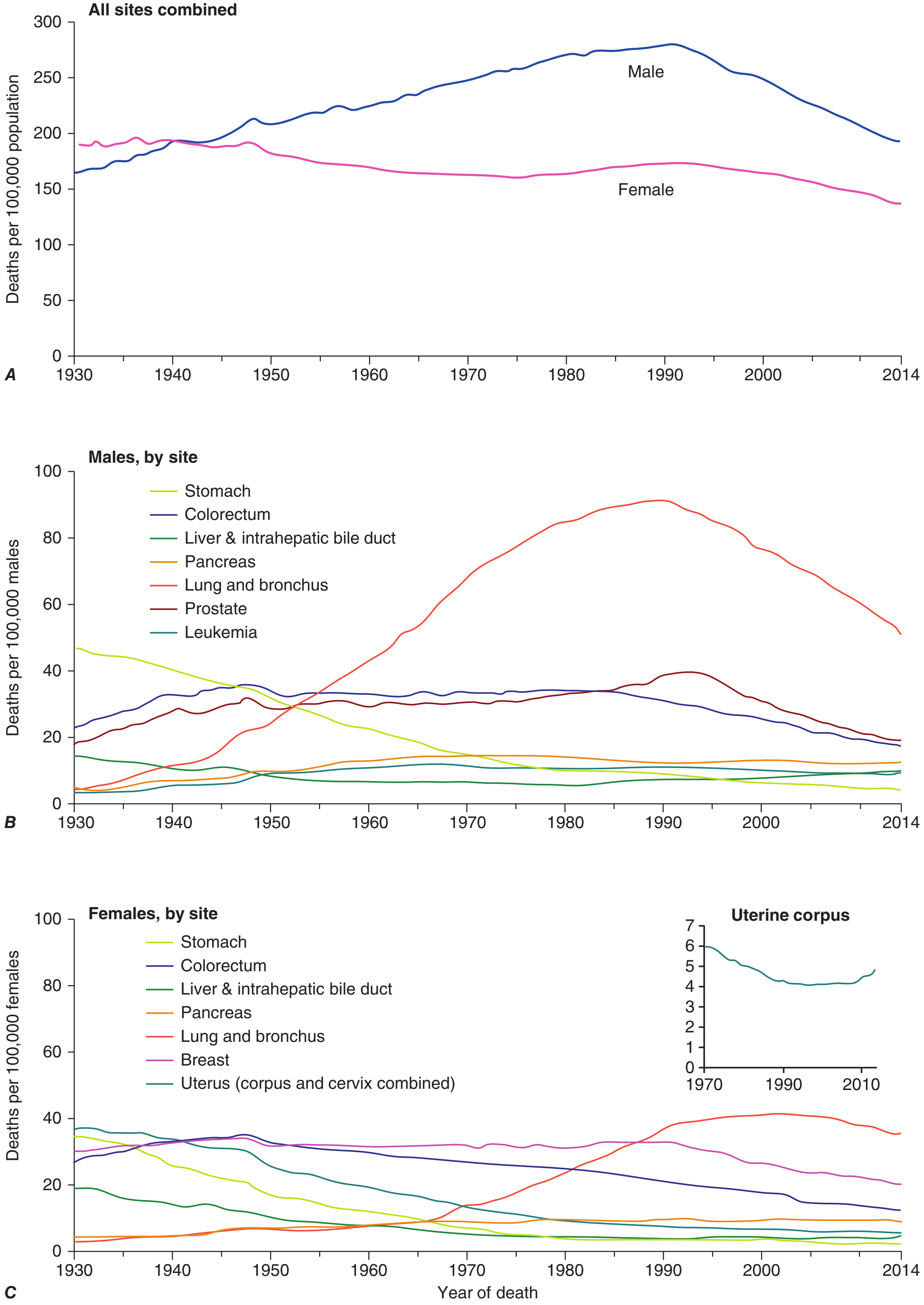


FIGURE II-3 An 85-year trend in cancer death rates for women and men by site in the United States from 1930 to 2014. Rates are per 100,000 age-adjusted to the 2000 U.S. standard population. All sites combined (***A***), individual sites in men (***B***), and individual sites in women (***C***) are shown. (Reproduced with permission from Siegel RL et al: Cancer statistics. *CA Cancer J Clin* 67:7, 2017.)

II-4. **The answer is B.** *(Chap. 65)* Although tumor burden is certainly a major factor in determining cancer outcomes, it is also important to consider the functional status of the patient when generating a therapeutic plan. The physiologic stresses of undergoing surgical interventions, radiation therapy, and chemotherapy can exhaust the limited reserves of a patient with multiple medical problems. It is clearly difficult to adequately measure the physiologic reserves of a patient, and most oncologists use performance status measures as a surrogate. Two of the most commonly used measures of performance status are the Eastern Cooperative Oncology Group (ECOG) and Karnofsky performance status. The ECOG scale provides a grade between 0 (fully active) and 5 (dead). Most patients are considered to have adequate reserve for undergoing treatment if the performance status is 0–2, with a status of 2 indicated in someone who is ambulatory and capable of self-care but unable to carry out work activities. These individuals are up and about more than 50% of waking hours. A grade 3 performance score would indicate someone who is capable of only limited self-care and is confined to a bed or chair more than 50% of waking hours. The Karnofsky score ranges from 0 (dead) to 100 (normal) and is graded at 10-point intervals. A Karnofsky score of <70 also indicates someone with poor performance status and would confer a worse prognosis.

II-5. **The answer is B.** *(Chap. 66)* Mammography is recommended (grade B recommendation) in women ages 50–74 years old, every 2 years. Colon cancer screening (Answer A) is recommended by the U.S. Preventive Services Task Force (USPSTF) to start at age 50. In the absence of a family history and in someone not having any symptoms, 44-years-old is earlier than the recommended age to begin colon cancer screening. Pap screening is not recommended after age 65 provided adequate negative prior screening. Screening for lung cancer with low-dose CT is recommended for adults aged 55–80 years old, with ≥30 pack-year smoking history, who are still smoking or have quit within the past 15 years. Chest x-rays are not the preferred imaging modality for lung cancer screening. The patient described in E has symptoms of prostate cancer so prostate-specific antigen testing would be considered an diagnostic test, not a screening test. Screening recommendations are for asymptomatic subjects (Table II-5) not known to be at increased risk for the target condition.

TABLE II-5 Screening Recommendations for Asymptomatic Subjects Not Known to Be at Increased Risk for the Target Condition[a]

Cancer Type	Test or Procedure	USPSTF	ACS
Breast	Self-examination	“D”[b] (Not in current recommendations; from 2009)	Women, all ages: No specific recommendation
	Clinical examination	Women ≥40 years: “I” (as a stand-alone without mammography) (Not in current recommendations; from 2009)	Women, all ages: Do not recommend
	Mammography	Women 40–49 years: The decision to start screening mammography in women prior to age 50 years should be an individual one. Women who place a higher value on the potential benefit than the potential harms may choose to begin biennial screening between the ages of 40 and 49 years. (“C”)	Women 40–44 years: Provide the opportunity to begin annual screening Women 45–54 years: Screen annually Women ≥55 years: Transition to biennial screening or have the opportunity to continue annual screening Women ≥40 should continue screening mammography as long as their overall health is good and they have a life expectancy of 10 years or longer
		Women 50–74 years: Every 2 years (“B”)	
		Women ≥75 years: “I”	
	MRI	“I” (Not in current recommendations; from 2009)	Women with >20% lifetime risk of breast cancer: Screen with MRI plus mammography annually
			Women with 15–20% lifetime risk of breast cancer: Discuss option of MRI plus mammography annually
			Women with <15% lifetime risk of breast cancer: Do not screen annually with MRI
	Tomosynthesis	Women, all ages: “I”	No specific recommendation

(*continued*)

TABLE II-5 Screening Recommendations for Asymptomatic Subjects Not Known to Be at Increased Risk for the Target Condition[a] (*Continued*)

Cancer Type	Test or Procedure	USPSTF	ACS
Cervical	Pap test (cytology)	Women 21–65 years: Screen every 3 years (“A”)	Women 21–29 years: Screen every 3 years
		Women <21 years: “D” Women >65 years, with adequate, normal prior Pap screenings: “D”	Women 30–65 years: Acceptable approach to screen with cytology every 3 years (see HPV test below) Women <21 years: No screening Women >65 years: No screening following adequate negative prior screening
		Women after total hysterectomy for noncancerous causes: “D”	Women after total hysterectomy for noncancerous causes: Do not screen
	HPV test	Women 30–65 years: Screen in combination with cytology every 5 years if woman desires to lengthen the screening interval (see Pap test above) (“A”) Women <30 years: “D” Women >65 years, with adequate, normal prior Pap screenings: “D” Women after total hysterectomy for noncancerous causes: “D”	Women 30–65 years: Preferred approach to screen with HPV and cytology co-testing every 5 years (see Pap test above) Women <30 years: Do not use HPV testing Women >65 years: No screening following adequate negative prior screening Women after total hysterectomy for noncancerous causes: Do not screen
Colorectal	Sigmoidoscopy	Adults, 50–75 years: “A” Screen for colorectal cancer; the risks and benefits of the different screening methods vary Adults, 76 to 85 years: “C” The decision to screen should be an individual one, taking into account the patient’s overall health and prior screening history Every 5 years; modeling suggests improved benefit if performed every 10 years in combination with annual FIT	Adults ≥50 years: Screen every 5 years
	FOBT	Every year	Adults ≥50 years: Screen every year
	Colonoscopy	Every 10 years	Adults ≥50 years: Screen every 10 years
	Fecal DNA testing	Every 1 or 3 years	Adults ≥50 years: Screen, but interval uncertain
	FIT	Every year	Adults ≥50 years: Screen every year
	CT colonography	Every 5 years	Adults ≥50 years: Screen every 5 years
Lung	Low-dose CT scan	Adults 55–80 years, with a ≥30 pack-year smoking history, still smoking or have quit within past 15 years: “B” Discontinue once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability to have curative lung surgery	Men and women, 55–74 years, with ≥30 pack-year smoking history, still smoking or have quit within past 15 years: Discuss benefits, limitations, and potential harms of screening; only perform screening in facilities with the right type of CT scanner and with high expertise/specialists
Ovarian	CA-125	Women, all ages: “D”	There is no sufficiently accurate test proven effective in the early detection of ovarian cancer For women at high risk of ovarian cancer and/or who have unexplained, persistent symptoms, the combination of CA-125 and transvaginal ultrasound with pelvic examination may be offered
	Transvaginal ultrasound	Women, all ages: “D”	
Prostate	PSA	Men, all ages: “D”	Starting at age 50, men should talk to a doctor about the pros and cons of testing so they can decide if testing is the right choice for them If African American or have a father or brother who had prostate cancer before age 65, men should have this talk starting at age 45 How often they are tested will depend on their PSA level

(*continued*)

TABLE II-5 **Screening Recommendations for Asymptomatic Subjects Not Known to Be at Increased Risk for the Target Condition**[a] **(*Continued*)**

Cancer Type	Test or Procedure	USPSTF	ACS
	DRE	No individual recommendation	As for PSA; if men decide to be tested, they should have the PSA blood test with or without a rectal examination
Skin	Complete skin examination by clinician or patient	Adults, all ages: "I"	Self-examination monthly; clinical examination as part of routine cancer-related checkup

[a] Summary of the screening procedures recommended for the general population by the USPSTF and the ACS. These recommendations refer to asymptomatic persons who are not known to have risk factors, other than age or gender, for the targeted condition.

[b] USPSTF lettered recommendations are defined as follows: A: The USPSTF recommends the service, because there is high certainty that the net benefit is substantial; B: The USPSTF recommends the service, because there is high certainty that the net benefit is moderate or moderate certainty that the net benefit is moderate to substantial; C: The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences, and there is at least moderate certainty that the net benefit is small; D: The USPSTF recommends against the service because there is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits; I: The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service.

Abbreviations: ACS, American Cancer Society; CT, computed tomography; DRE, digital rectal examination; FIT, fecal immunochemical test; FOBT, fecal occult blood test; HPV, human papillomavirus; MRI, magnetic resonance imaging; PSA, prostate-specific antigen; USPSTF, U.S. Preventive Services Task Force.

II-6. **The answer is D.** *(Chap. 66) Sensitivity*, also called the true-positive rate, is the proportion of persons with the disease who test positive in the screening test (i.e., the ability of the test to detect disease when it is present). In the case presented, there are 8 true positives and 2 false negatives (10 total people with the disease), which gives a sensitivity of 80%. *Specificity*, or 1 minus the false-positive rate, is the proportion of persons who do not have the disease that test negative in the screening test (i.e., the ability of a test to correctly indicate that the disease is not present). In this case, the false positive rate is 6%; therefore, the specificity is 94%. The sensitivity and specificity of a test are independent of the underlying prevalence (or risk) of the disease in the population screened, but the predictive values depend strongly on the prevalence of the disease.

II-7. **The answer is C.** *(Chap. 67)* The normal role of tumor-suppressor genes is to restrain cell growth, and the function of these genes is inactivated in many cancers. The three major types of somatic lesions observed in tumor-suppressor genes during tumor development are *point mutations*, small insertions and/or deletions known as *indels*, and *large deletions*. Point mutations or indels in the coding region of tumor-suppressor genes will frequently lead to truncated protein products or allele-specific loss of RNA expression by the process of *nonsense-mediated decay*. Unlike the highly recurrent point mutations that are found in critical positions of activated oncogenes, known as mutational *hotspots*, the point mutations that cause tumor-suppressor gene inactivation tend to be distributed throughout the open reading frame. Large deletions lead to the loss of a functional product and sometimes encompass the entire gene or even the entire chromosome arm, leading to loss of heterozygosity (LOH) in the tumor DNA compared with the corresponding normal tissue DNA (Figure II-7). Solid tumors generally contain an abnormal number of chromosomes, a state known as aneuploidy; chromosomes from aneuploid tumors exhibit structural alterations such as translocations, deletions, and amplifications. These abnormalities reflect an underlying defect in cancer cells known as chromosomal instability. While aneuploidy is a striking cellular phenotype, chromosomal instability is manifest as only a small increase in the tendency of cells to gain, lose, or rearrange chromosomes during any given cell cycle. Point mutation (alternatively known as single nucleotide substitution) is a common mechanism of oncogene activation. The restricted pattern of mutations observed in oncogenes compared with that of tumor-suppressor genes reflects the fact that gain-of-function mutations must occur at specific sites, whereas a broad variety of mutations can lead to loss of activity. Gene silencing, an epigenetic change that leads to the loss of gene expression, occurs in conjunction with hypermethylation of the promoter and histone deacetylation, and

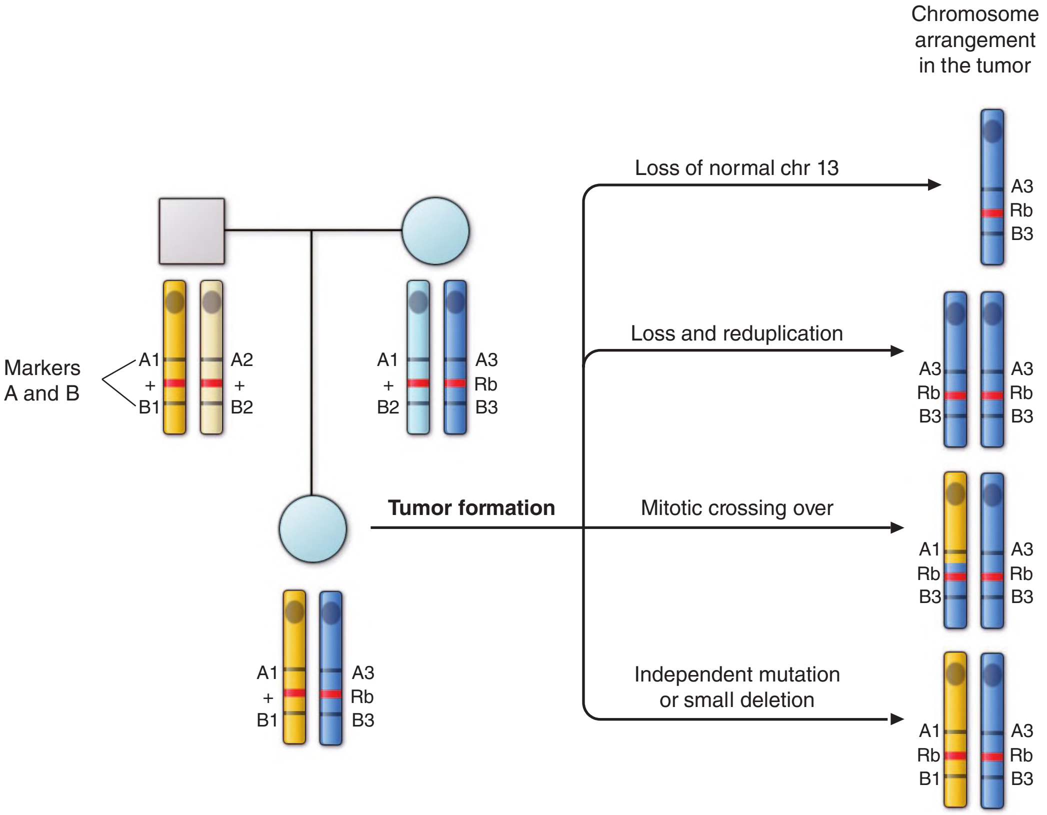


FIGURE II-7 Diagram of possible mechanisms for tumor formation in an individual with hereditary (familial) retinoblastoma. On the left is shown the pedigree of an affected individual who has inherited the abnormal (Rb) allele from her affected mother. The normal allele is shown as a (+). The four chromosomes of her two parents are drawn to indicate their origin. Flanking the retinoblastoma locus are genetic markers (A and B) also analyzed in this family. Markers A3 and B3 are on the chromosome carrying the retinoblastoma disease gene. Tumor formation results when the normal allele, which this patient inherited from her father, is inactivated. On the right are shown four possible ways in which this could occur. In each case, the resulting chromosome 13 arrangement is shown. Note that in the first three situations, the normal allele (B1) has been lost in the tumor tissue, which is referred to as loss of heterozygosity (LOH) at this locus.

is another mechanism of tumor-suppressor gene inactivation. An *epigenetic modification* refers to a covalent modification of chromatin, heritable by cell progeny that may involve DNA but does not involve a change in the DNA sequence.

II-8. **The answer is D.** *(Chap. 67)* An algorithm for cancer risk assessment and decision-making in high-risk families using genetic testing is shown in Figure II-8. Patients who are from a family with a known cancer syndrome, from a family with a history of cancer, or have an early onset of cancer should undergo retest counseling. In patients lacking a clear family history (in this case, with a single family member who had a clear environmental exposure), the significance of these DNA sequence findings will not be apparent. Even mutations in tumor-suppressor genes are difficult to interpret unless there is an obvious functional implication, such as the truncation of the open reading frame, or that particular mutation has previously been associated with cancer. Once a mutation is discovered in a family, subsequent testing of asymptomatic family members can be crucial in patient management. A negative gene test in these individuals can prevent years of anxiety in the knowledge that their cancer risk is no higher than that of the general population. On the other hand, a positive test may lead to alteration of clinical management, such as increased frequency of cancer screening and, when feasible and appropriate, prophylactic surgery. Potential negative consequences of a positive test result include psychological distress (anxiety, depression) and discrimination, although the Genetic Information Nondiscrimination Act makes it illegal for predictive genetic information to be used to discriminate in health insurance or employment. Testing should therefore not be conducted without counseling before and after disclosure of the test result. Age and cancer screening are not relevant to the decision to undergo genetic testing.

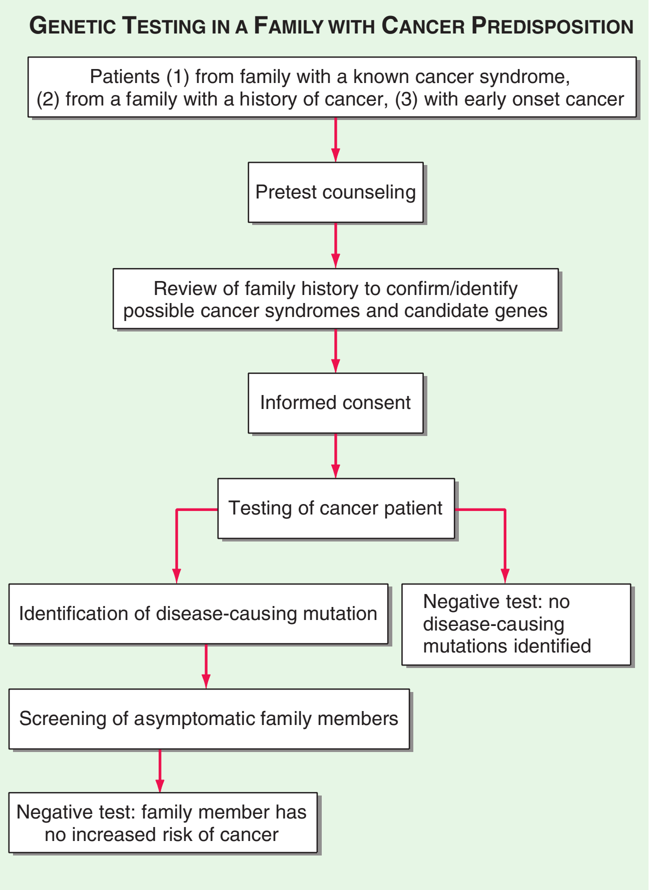

GENETIC TESTING IN A FAMILY WITH CANCER PREDISPOSITION
Patients (1) from family with a known cancer syndrome, (2) from a family with a history of cancer, (3) with early onset cancer
Pretest counseling
Review of family history to confirm/identify possible cancer syndromes and candidate genes
Informed consent
Testing of cancer patient
Identification of disease-causing mutation
Negative test: no disease-causing mutations identified
Screening of asymptomatic family members
Negative test: family member has no increased risk of cancer

FIGURE II-8 Algorithm for genetic testing in a family with cancer predisposition. The key step is the identification of a disease mutation in a cancer patient, which is an indication for the testing of asymptomatic family members. Asymptomatic family members who test positive may require increased screening or surgery, whereas those who test negative are at no greater risk for cancer than the general population. It should be emphasized that no molecular assay used for this sort of testing is 100% sensitive; negative results must be interpreted with this caveat in mind.

II-9. **The answer is D.** *(Chap. 68)* Cancers have a number of mechanisms that allow them to evade detection and elimination by the immune system (Figure II-9). These include downregulation of cell surface proteins involved in immune recognition (including major histocompatibility complex proteins and tumor-specific antigens), expression of other cell surface proteins that inhibit immune function (including CTLA-4, PD-L1), secretion of proteins, immunosuppressive cytokines and other molecules that are immunosuppressive, recruitment and expansion (not downregulation) of immunosuppressive cells such as regulatory T cells and macrophages, induction of T-cell tolerance, downregulation of death receptors, and disruption of cell signaling. Due to the marked heterogeneity of cells within a cancer, a variety of immune suppressive mechanisms are continuously occurring and changing. In addition, the inflammatory effects of some of the immune mediator cells in the tumor microenvironment (especially tissue-associated macrophages and myeloid-derived suppressor cells) can suppress T-cell responses to the tumor as well as stimulate inflammation that can enhance tumor growth. Cancer therapy has changed recently to include immunotherapy, which is aimed at activating the immune response against tumors using immunostimulatory molecules such as interferons, interleukin-2, and monoclonal antibodies targeting mechanisms mentioned above.

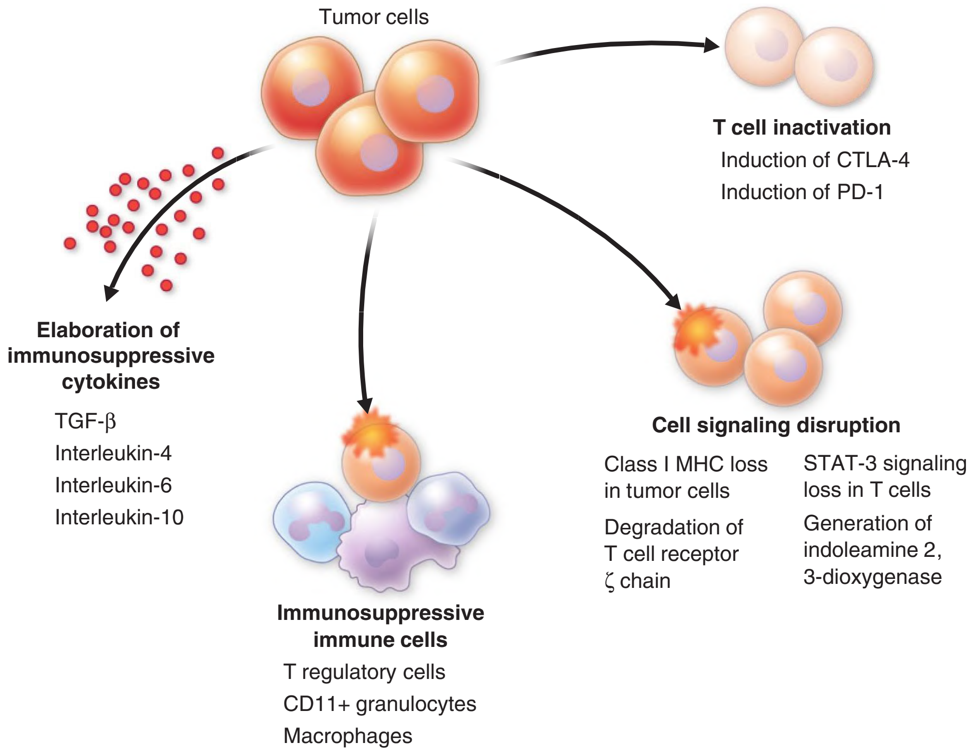

Tumor cells
T cell inactivation
Induction of CTLA-4
Induction of PD-1
Elaboration of immunosuppressive cytokines
TGF-β
Interleukin-4
Interleukin-6
Interleukin-10
Cell signaling disruption
Class I MHC loss in tumor cells
Degradation of T cell receptor ζ chain
STAT-3 signaling loss in T cells
Generation of indoleamine 2, 3-dioxygenase
Immunosuppressive immune cells
T regulatory cells
CD11+ granulocytes
Macrophages

FIGURE II-9 Tumor-host interactions that suppress the immune response to the tumor. *Abbreviations:* MHC, major histocompatibility complex; TGF, transforming growth factor.

II-10. **The answer is A.** *(Chap. 69)* Escalating doses of the drug are then given during the human phase I trial until reversible toxicity is observed. Dose-limiting toxicity (DLT) defines a dose that conveys greater toxicity than would be acceptable in routine practice, allowing definition of a lower maximum-tolerated dose (MTD). The MTD or a dose just lower than the MTD is usually the dose suitable for phase II trials, where a fixed dose is administered to a relatively homogeneous set of patients with a particular tumor type in an effort to define whether the drug causes regression of tumors. In a phase III trial, evidence of improved overall survival or improvement in the time to progression of disease on the part of the new drug is sought compared with an appropriate control population, which is usually receiving an acceptable "standard-of-care" approach. A favorable outcome of a phase III trial is the basis for application to a regulatory agency for approval of the new agent for commercial marketing as safe and possessing a measure of clinical effectiveness. Phase IV trial relates to post-marketing studies.

II-11. **The answer is E.** *(Chap. 70)* Patients who have undergone allogeneic stem cell transplantation remain at risk for infectious complications for an extended period despite engraftment and apparent return of normal hematopoietic capacity. Individuals with graft-versus-host disease (GVHD) often require immunosuppressive treatment that further increases infectious risk. Prevention of infection is the goal in these individuals, and the clinician should ensure appropriate vaccinations for all patients who have undergone intensive chemotherapy, have been treated for Hodgkin disease, or have undergone hematopoietic stem cell transplantation. In hematopoietic stem cell transplantations, the time line for vaccination varies after transplantation. Diphtheria-tetanus-pertussis, poliomyelitis, *Haemophilus influenzae* type b conjugate, and hepatitis B are all given in 3 doses, 6–12 months after transplantation. Human papillomavirus vaccine is approved for males and females 9–26 years of age. Seasonal influenza vaccine can be given as early as 4 months after transplantation. If given less than 6 months after transplantation, an additional dose is recommended. Varicella-zoster virus vaccine, a live virus vaccine, is contraindicated in patients who have received hematopoietic stem cell transplantation. Additionally, measles/mumps/rubella vaccine should only be given after 24 months in patients without GVHD. A summary of vaccination recommendations for cancer patients receiving chemotherapy is shown in Table II-11.

TABLE II-11 Vaccination of Cancer Patients Receiving Chemotherapy[a]

	Use in Indicated Patients		
Vaccine	Intensive Chemotherapy	Hodgkin Disease	Hematopoietic Stem Cell Transplantation
Diphtheria-tetanus-pertussis[b]	Primary series and boosters as necessary	No special recommendation	3 doses given 6–12 months after transplantation
Poliomyelitis[c]	Complete primary series and boosters	No special recommendation	3 doses given 6–12 months after transplantation
Haemophilus influenzae type b conjugate	Primary series and booster for children	Single dose for adults	3 doses given 6–12 months after transplantation (separated by 1 month)
HPV	HPV vaccine is approved for males and females 9–26 years of age Check the CDC website (*www.cdc.gov/vaccines*) for updated recommendation.	HPV vaccine is approved for males and females 9–26 years of age Check the CDC website (*www.cdc.gov/vaccines*) for updated recommendations	HPV vaccine is approved for males and females 9–26 years of age Check the CDC website (*www.cdc.gov/vaccines*) for updated recommendations
Hepatitis A	As indicated for normal hosts on the basis of occupation and lifestyle	As indicated for normal hosts on the basis of occupation and lifestyle	As indicated for normal hosts on the basis of occupation and lifestyle
Hepatitis B	Same as for normal hosts	As indicated for normal hosts on the basis of occupation and lifestyle	3 doses given 6–12 months after transplantation
Pneumococcal conjugate vaccine (PCV13) Pneumococcal polysaccharide vaccine (PPSV23)[d]	Finish series prior to chemotherapy if possible	Patients with splenectomy should receive both PCV13 and PPSV23	Three doses of PCV13, beginning 3–6 months after transplantation, are followed by a dose of PPSV23 at least 8 weeks later A second PPSV23 dose can be given 5 years later
Quadrivalent meningococcal vaccine[e] Meningococcal B vaccine	Should be administered to splenectomized patients and to patients living in endemic areas, including college students in dormitories See above	Should be administered to splenectomized patients and to patients living in endemic areas, including college students in dormitories An additional dose can be given after 5 years. See above	Should be administered to splenectomized patients and to patients living in endemic areas, including college students in dormitories An additional dose can be given after 5 years See above (see *www.cdc.gov/vaccines* for updated recommendations).
Influenza	Seasonal immunization	Seasonal immunization	Seasonal immunization (a seasonal dose is recommended and can be given as early as 4 months after transplantation; if given <6 months after transplantation, an additional dose is recommended).
Measles/mumps/rubella	Contraindicated	Contraindicated during chemotherapy	After 24 months in patients without graft-versus-host disease
Varicella-zoster virus[f]	Contraindicated[g]	Contraindicated	Contraindicated (CDC recommends use on a case-by-case basis following reevaluation.)

[a] The latest recommendations by the Advisory Committee on Immunization Practices and the CDC guidelines can be found at *www.cdc.gov/vaccines*.

[b] A single dose of tetanus–diphtheria–acellular pertussis A(TDaP), followed by a booster dose of tetanus–diphtheria (Td) every 10 years, is recommended for adults.

[c] Live-virus vaccine is contraindicated; inactivated vaccine should be used.

[d] Two types of vaccines are used to prevent pneumococcal disease. A conjugate vaccine active against 13 serotypes (13-valent pneumococcal conjugate vaccine, or PCV13) is currently administered in three separate doses to all children. A polysaccharide vaccine active against 23 serotypes (23-valent pneumococcal polysaccharide vaccine, or PPSV23) elicits titers of antibody lower than those achieved with the conjugate vaccine, and immunity may wane more rapidly. Because the ablative chemotherapy given to recipients of hematopoietic stem cell transplants (HSCTs) eradicates immunologic memory, revaccination is recommended for all such patients. Vaccination is much more effective once immunologic reconstitution has occurred; however, because of the need to prevent serious disease, pneumococcal vaccine should be administered 6–12 months after transplantation in most cases. Because PPSV23 includes serotypes not present in PCV13, HSCT recipients should receive a dose of PPSV23 at least 8 weeks after the last dose of PCV13. Although antibody titers from PPSV23 clearly decay, experience with multiple doses of PPSV23 is limited, as are data on the safety, toxicity, or efficacy of such a regimen. For this reason, the CDC currently recommends the administration of one additional dose of PPSV23 at least 5 years after the last dose to immunocompromised patients, including transplant recipients, as well as patients with Hodgkin disease, multiple myeloma, lymphoma, or generalized malignancies. Beyond this single additional dose, further doses are not recommended at this time.

[e] Meningococcal conjugate vaccine (MenACWY) is recommended for adults ≤55 years old, and meningococcal polysaccharide vaccine (MPSV4) is recommended for those ≥56 years old.

[f] Includes both varicella vaccine for children and zoster vaccine for adults.

[g] Contact the manufacturer for more information on use in children with acute lymphocytic leukemia.

Abbreviations: CDC, Centers for Disease Control and Prevention; HPV, human papillomavirus.

II-12. **The answer is D.** *(Chap. 70)* Neutropenic patients are unusually susceptible to infection with a wide variety of bacteria; thus, in the presence of fever and presumed infection, IV broad-spectrum antibiotic therapy should be initiated promptly to cover likely pathogens if infection is suspected. Indeed, early initiation of antibacterial agents is mandatory to prevent death in these susceptible patients. Like most immunocompromised patients, neutropenic patients are threatened by their own microbial flora, including gram-positive and gram-negative organisms found commonly on the skin and mucous membranes and in the bowel (Table II-12). Because treatment with narrow-spectrum agents may not treat all likely infectious agents with the initial regimen, it should target all pathogens likely to be the initial causes of bacterial infection in neutropenic hosts. Randomized trials have indicated the safety of oral antibiotic regimens in the treatment of "low-risk" patients with fever and neutropenia. Outpatients who are expected to

TABLE II-12 **Organisms Likely to Cause Infections in Granulocytopenic Patients**

Gram-Positive Cocci	
Staphylococcus epidermidis	*Staphylococcus aureus*
Viridans *Streptococcus*	*Enterococcus faecalis*
Streptococcus pneumoniae	
Gram-Negative Bacilli	
Escherichia coli	*Serratia* spp.
Klebsiella spp.	*Acinetobacter* spp.[a]
Pseudomonas aeruginosa	*Stenotrophomonas* spp.
Enterobacter spp.	*Citrobacter* spp.
Non-*aeruginosa Pseudomonas* spp.[a]	
Gram-Positive Bacilli	
Diphtheroids	JK bacillus[a]
Fungi	
Candida spp.	*Mucor/Rhizopus*
Aspergillus spp.	

[a] Often associated with IV catheters.

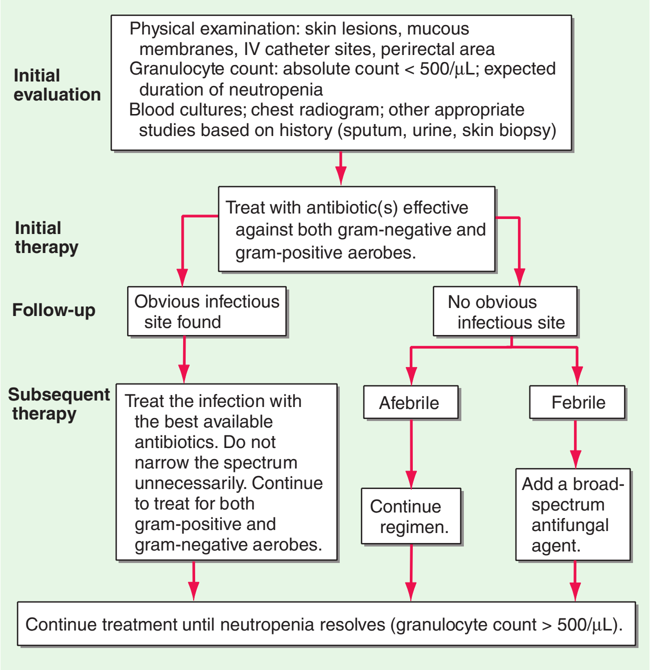

Initial evaluation
Physical examination: skin lesions, mucous membranes, IV catheter sites, perirectal area
Granulocyte count: absolute count < 500/µL; expected duration of neutropenia
Blood cultures; chest radiogram; other appropriate studies based on history (sputum, urine, skin biopsy)
Initial therapy
Treat with antibiotic(s) effective against both gram-negative and gram-positive aerobes.
Follow-up
Obvious infectious site found
No obvious infectious site
Subsequent therapy
Treat the infection with the best available antibiotics. Do not narrow the spectrum unnecessarily. Continue to treat for both gram-positive and gram-negative aerobes.
Afebrile
Febrile
Continue regimen.
Add a broad-spectrum antifungal agent.
Continue treatment until neutropenia resolves (granulocyte count > 500/µL).

FIGURE II-12 Algorithm for the diagnosis and treatment of fever and neutropenia. *Abbreviations:* IV, intravenous.

remain neutropenic for <10 days and who have no concurrent medical problems (such as hypotension, pulmonary compromise, or abdominal pain) can be classified as low risk and treated with a broad-spectrum oral regimen. This patient would not qualify as low risk due to symptoms, hypotension, and tachycardia. Therefore IV therapy is indicated. As noted in the algorithm (Figure II-12) administration of antimicrobial agents is routinely continued until neutropenia resolves; that is, the granulocyte count is sustained above 500/μL for at least 2 days. Fever may not resolve prior to granulocyte recovery. In some cases, patients remain febrile after resolution of neutropenia. In these instances, the risk of sudden death from overwhelming bacteremia is greatly reduced, and the following diagnoses should be seriously considered: (1) fungal infection, (2) bacterial abscesses or undrained foci of infection, and (3) drug fever (including reactions to antimicrobial agents as well as to chemotherapy or cytokines). In the proper setting, viral infection or graft-versus-host disease should be considered. In clinical practice, antibacterial therapy is usually discontinued when the patient is no longer neutropenic and all evidence of bacterial disease has been eliminated.

II-13. **The answer is D.** *(Chap. 70)* Clinicians are often faced with treatment decisions regarding potential catheter-related infections in patients who are immunocompromised from cancer and chemotherapy. Because many patients require several weeks of chemotherapy, tunneled catheters are often placed, and determining the need for catheter removal is an important consideration. When blood cultures are positive or there is evidence of infection along the track of the tunnel, catheter removal is recommended. When the erythema is limited to the exit site only, then it is not necessary to remove the catheter unless the erythema fails to respond to treatment. The recommended treatment for an exit site infection should be directed against coagulase-negative staphylococci. In the options presented, vancomycin alone is the best option for treatment. There is no need to add therapy for gram-negative organisms because the patient does not have neutropenia and has negative cultures.

II-14. **The answer is B.** *(Chap. 71)* Malignant pericardial disease is found at autopsy in 5–10% of patients with cancer, most frequently with lung cancer, breast cancer, leukemias, and lymphomas. Cardiac tamponade as the initial presentation of extrathoracic malignancy is rare. The origin is not malignancy in ~50% of cancer patients with symptomatic pericardial disease, but it can be related to irradiation, drug-induced pericarditis (including chemotherapeutic agents such all-trans retinoic acid, arsenic trioxide, imatinib, and other Abl kinase inhibitors), hypothyroidism, idiopathic pericarditis, infection, or autoimmune diseases. The three principal features of tamponade (*Beck's triad*) are hypotension, soft or absent heart sounds, and jugular venous distention with a prominent *x* (early systolic) descent but an absent *y* (early diastolic) descent. The limitations to ventricular filling are responsible for reductions of cardiac output and arterial pressure. The quantity of fluid necessary to produce cardiac tamponade may be as small as 200 mL when the fluid develops rapidly to as much as >2000 mL in slowly developing effusions when the pericardium has had the opportunity to stretch and adapt to an increasing volume. The common symptoms of pericardial tamponade are dyspnea, cough, chest pain, orthopnea, and weakness. Pleural effusion, sinus tachycardia, jugular venous distention, hepatomegaly, peripheral edema, and cyanosis are the most frequent physical findings. Relatively specific diagnostic findings, such as paradoxic pulse, diminished heart sounds, pulsus alternans (pulse waves alternating between those of greater and lesser amplitude with successive beats), and friction rub are less common with malignant pericardial effusions than with nonmalignant pericardial disease. Chest radiographs and electrocardiogram reveal abnormalities in 90% of patients, but half of these abnormalities are nonspecific. Echocardiography is the most helpful diagnostic test. A high index of suspicion for cardiac tamponade is required because in many instances no obvious cause for pericardial disease is apparent, and this diagnosis should be considered in any patient with otherwise unexplained sudden enlargement of the cardiac silhouette, hypotension, and elevation of jugular venous pressure. Based on the physical examination findings, it is unlikely that imaging would be normal or reveal entire opacification of the right hemithorax. Whereas evidence of a thoracic malignancy is likely to be identified, the position and involvement described with involvement of the brachial plexus is also likely to produce superior vena cava syndrome, which is not described here. Pneumothorax can be associated with lung cancer; however, the physical examination described here does not support that diagnosis.

II-15. **The answer is E.** *(Chaps. 71 and 265)* Pericardiocentesis with or without the introduction of sclerosing agents, the creation of a pericardial window, complete pericardial stripping, cardiac irradiation, or systemic chemotherapy are effective treatments for pericardial tamponade due to a malignant effusion. Acute pericardial tamponade with life-threatening hemodynamic instability requires immediate drainage of fluid. This can be quickly achieved by pericardiocentesis. The recurrence rate after percutaneous catheter drainage is ~20%. Sclerotherapy (pericardial instillation of bleomycin, mitomycin C, or tetracycline) may decrease recurrence. Alternatively, subxiphoid pericardiotomy can be performed quickly under local anesthesia. Thoracoscopic pericardial fenestration can be employed for benign causes; however, 60% of malignant pericardial effusions recur after this procedure. In a subset of patients, drainage of the pericardial effusion is paradoxically followed by worsening hemodynamic instability. This so-called "postoperative low cardiac output syndrome" occurs in up to 10% of patients undergoing surgical drainage and carries poor short-term survival. Treatment for superior vena cava syndrome, which can present similarly, would include diuretics, radiation, and chemotherapy. Early stenting may be necessary in patients with severe symptoms. Antibiotics are unlikely to be helpful as there is a low suspicion for acute infection. Neither chemotherapy nor radiotherapy would be indicated in this case prior to a tissue diagnosis.

II-16. **The answer is A.** *(Chap. 71)* This patient presents with symptoms of spinal cord compression in the setting of known stage IV breast cancer. This represents an oncologic emergency as only 10% of patients presenting with paraplegia regain the ability to walk. Most commonly, patients develop symptoms of localized back pain and tenderness days to months before developing paraplegia. The pain is worsened by movement, cough, or sneezing. In contrast to radicular pain, the pain related to spinal cord metastases is worse with lying down. Patients presenting with back pain alone should have a careful examination to attempt to localize the lesion prior to development of more severe neurologic symptoms. In this patient with paraplegia, there is a definitive level at which sensation is diminished. This level is typically one to two vertebrae below the site of compression. Other findings include spasticity, weakness, and increased deep tendon reflexes. In those with autonomic dysfunction, bowel and bladder incontinence will occur with decreased anal tone, absence of the anal wink and bulbocavernosus reflexes, and bladder distention. The most important initial step is the administration of high-dose IV corticosteroids to minimize associated swelling around the lesion and prevent paraplegia while allowing further evaluation and treatment. An MRI of the entire spinal cord should be performed to evaluate for other metastatic disease that may require therapy. Although a brain MRI may be indicated in the future to evaluate for brain metastases, it is not required in the initial evaluation because the bilateral nature of the patient's symptoms and sensory level clearly indicate the spinal cord as the site of the injury. Once an MRI is performed, a definitive treatment plan can be made. Most commonly, radiation therapy is used with or without surgical decompression.

II-17. and II-18. **The answers are B and E, respectively.** *(Chap. 71)* Tumor lysis syndrome occurs most commonly in individuals undergoing chemotherapy for rapidly proliferating malignancies, including acute leukemias and Burkitt lymphoma. In rare instances, it can be seen in chronic lymphoma or solid tumors. As the chemotherapeutic agents act on these cells, there is massive tumor lysis that results in release of intracellular ions and nucleic acids. This leads to a characteristic metabolic syndrome of hyperuricemia, hyperphosphatemia, hyperkalemia, and hypocalcemia. Acute kidney injury is frequent and can lead to renal failure requiring hemodialysis if uric acid crystallizes within the renal tubules. Lactic acidosis and dehydration increase the risk of acute kidney injury. Hyperphosphatemia occurs due to the release of intracellular phosphate ions and causes a reciprocal reduction in serum calcium. The hypocalcemia can be profound, leading to neuromuscular irritability and tetany. Hyperkalemia can become rapidly life-threatening and cause ventricular arrhythmia. Knowing the characteristics of tumor lysis syndrome, one can attempt to prevent the known complications from occurring. It is important to monitor serum electrolytes frequently during treatment. Laboratory studies should be obtained no less than three times daily, but more frequent monitoring is often needed. Allopurinol should be administered prophylactically at high doses. If allopurinol fails to control uric acid to less than 8 mg/dL, rasburicase, a recombinant urate oxidase, can be added at a dose of 0.2 mg/kg. Throughout this period, the patient should be intravenously well hydrated with alkalinization of the urine to a pH of greater than 7.0. Prophylactic hemodialysis is not performed unless there is underlying renal failure prior to starting chemotherapy.

II-19. **The answer is A.** *(Chap. 72)* Acral lentiginous melanoma is the most common melanoma in blacks, Asians, and Hispanics and occurs as an enlarging hyperpigmented macule or plaque on the palms and soles. Lentigo maligna melanoma occurs on sun-exposed skin as a large, hyperpigmented macule or plaque with irregular borders and variable pigmentation. As the bottom of the foot is not a skin-exposed area, this is less likely in this case. Dysplastic nevi are benign, irregularly pigmented and shaped melanocytic hamartomas with some atypical cellular features and frequently associated with familial melanoma. These would not be expected to increase in size over a short period of time. Impetigo is a common superficial bacterial infection of skin caused most often by *Staphylococcus aureus (Chap. 142)* and in some cases by group A β-hemolytic streptococci *(Chap. 143)*. The primary lesion is a superficial pustule that ruptures and forms a characteristic yellow-brown honey-colored crust. The lesions of secondary syphilis are initially pale red or pink nonpruritic discrete macules distributed on the trunk and extremities; these macules progress to papular lesions that are distributed widely and that frequently involve the palms and soles. A syphilitic lesion would not be expected to be a solitary isolated lesion on the sole.

II-20. **The answer is B.** *(Chap. 72)* The best predictor of metastatic risk in melanoma is Breslow thickness, which defines the absolute extent of tumor extension into the tissue. The Clark level defines the extent of invasion of the melanoma based on the layer of the skin involved but does not add significant prognostic information beyond the Breslow thickness. The number of mitoses is used in staging of tumors <1 mm in thickness to provide additional prognostic information about the likelihood of metastatic disease because patients with fewer mitoses have better long-term outcomes. Favorable anatomic sites for prognosis are the forearm and leg, with less favorable sites being the scalp, hands, feet, and mucous membranes. Women generally have better outcomes than men and are frequently diagnosed at earlier stages than men. The effect of age is not straightforward. Older patients are usually diagnosed with thicker primary tumors and have a later diagnosis, but younger patients have a greater risk of lymph node metastases.

II-21. **The answer is C.** *(Chap. 72)* Nonmelanoma skin cancer (NMSC) is the most common cancer in the United States, with an estimated annual incidence of 1.5–2 million cases yearly. However, most of these cases represent very limited disease with a low metastatic potential and account for only 2400 deaths yearly. The vast majority of NMSCs are basal cell carcinomas (BCCs; 70–80%) or squamous cell carcinomas (SCC; ~20%). The primary risk factor for all NMSCs is ultraviolet (UV) light exposure. UV exposure can occur either through direct exposure to sunlight (UVA and UVB exposure) or via tanning beds (97% UVA exposure). Other risk factors for NMSC include inherited disorders of nucleotide excision repair such as xeroderma pigmentosum, fair complexion, light hair/eyes, cigarette smoking, HIV infection, exposure to ionizing radiation, thermal burn scars, albinism, and chronic ulcerations. In addition, recipients of solid organ transplantations on chronic immunosuppression have a 65-fold increase in SCC and 10-fold increase in BCC. Moreover, NMSC in those with solid organ transplantation is more likely to be aggressive with higher rates of local recurrence, metastasis, and mortality. When comparing BCC with SCC, BCC is the less aggressive of the NMSCs and is typically a slowly enlarging, locally invasive neoplasm. The metastatic potential of BCC is <0.1%. SCC has a more variable natural history, depending on the lesion and host factors. Keratoacanthomas are rapidly growing, low-grade SCCs that can regress spontaneously without therapy. However, progression to metastatic disease has been reported after regression, so treatment for keratoacanthoma should be similar to that for other SCCs. Actinic keratoses and cheilitis are premalignant forms of SCC with transformation to malignancy occurring in 0.25–20%. In general, the metastatic potential of SCC ranges from 0.3–5.2%, with the greatest risk of metastases in tumors arising from non–sun-exposed tissues. The approach to treating NMSC depends on the size, depth, location, and host factors, with the primary goal being eradication of the tumor with wide local margins.

II-22. **The answer is E.** *(Chap. 73)* The number of new cases of head and neck cancers (oral cavity, pharynx, and larynx) in the United States was 48,330 in 2016, accounting for about 3% of adult malignancies; estimated deaths were 13,190. The worldwide incidence exceeds half a million cases annually. In North America and Europe, the tumors usually arise from the oral cavity, oropharynx, or larynx. The incidence of oropharyngeal cancers is increasing in recent years, especially in Western countries. Nasopharyngeal cancer is more commonly seen in the Mediterranean countries and in the Far East, where it is endemic in some areas. Alcohol and tobacco use are the most significant risk factors for head and neck cancer, and when used together, they act synergistically. Smokeless tobacco is an etiologic agent for oral cancers. Other potential carcinogens include marijuana and occupational exposures such as nickel refining, exposure to textile fibers, and woodworking. Some head and neck cancers have a viral etiology. Epstein-Barr virus infection is frequently associated with nasopharyngeal cancer, especially in endemic areas of the Mediterranean and Far East. In Western countries, the human papilloma virus is associated with a rising incidence of tumors arising from the oropharynx, that is, the tonsillar bed and base of tongue. Second head and neck malignancies are usually not therapy induced; they reflect the exposure of the upper aerodigestive mucosa to the same carcinogens that caused the first cancer. Rarely, patients can develop a radiation therapy–induced sarcoma after having undergone prior radiotherapy for a head and neck cancer.

II-23. **The answer is A.** *(Chap. 73)* Advanced head and neck cancers in any location can cause severe pain, otalgia, airway obstruction, cranial neuropathies, trismus, odynophagia, dysphagia, decreased tongue mobility, fistulas, skin involvement, and massive cervical lymphadenopathy, which may be unilateral or bilateral. Some patients have enlarged lymph nodes even though no primary lesion can be detected by endoscopy or biopsy; these patients are considered to have carcinoma of unknown primary. Tonsillectomy and directed biopsies of the base of tongue can frequently identify a small primary tumor that frequently will be HPV related. If the enlarged nodes are located in the upper neck and the

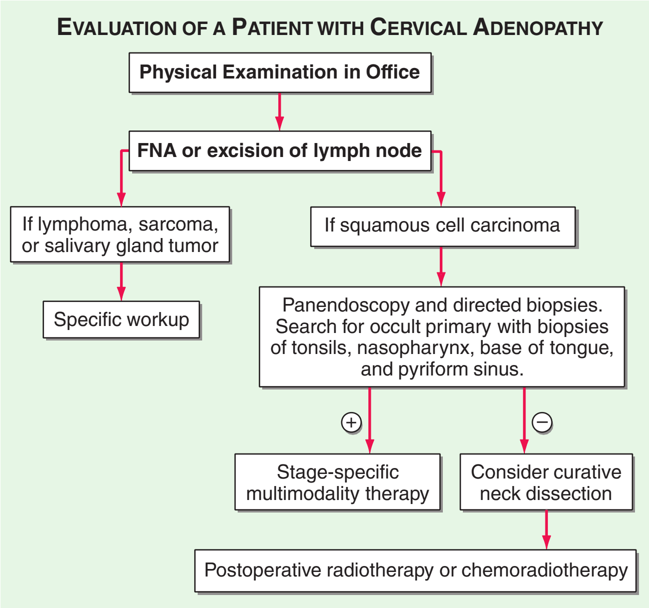

EVALUATION OF A PATIENT WITH CERVICAL ADENOPATHY
Physical Examination in Office
FNA or excision of lymph node
If lymphoma, sarcoma, or salivary gland tumor
If squamous cell carcinoma
Specific workup
Panendoscopy and directed biopsies. Search for occult primary with biopsies of tonsils, nasopharynx, base of tongue, and pyriform sinus.
+
−
Stage-specific multimodality therapy
Consider curative neck dissection
Postoperative radiotherapy or chemoradiotherapy

FIGURE II-23 Evaluation of a patient with cervical adenopathy without a primary mucosal lesion; a diagnostic workup. *Abbreviation:* FNA, fine-needle aspiration.

tumor cells are of squamous cell histology, the malignancy probably arose from a mucosal surface in the head or neck. Tumor cells in supraclavicular lymph nodes may also arise from a primary site in the chest or abdomen. The definitive staging procedure is an endoscopic examination under anesthesia, which may include laryngoscopy, esophagoscopy, and bronchoscopy; during this procedure, multiple biopsy samples are obtained to establish a primary diagnosis, define the extent of primary disease, and identify any additional premalignant lesions or second primaries. There are no specific tumor markers used in the diagnosis of head and neck cancers. Repeat biopsy would not be helpful unless the first one was nondiagnostic, which is not the case here. A positron emission tomography (PET) scan may also be administered and can help to identify or exclude distant metastases but is typically done after a primary site is identified. CT and PET scans may also be useful in evaluating response to therapy. Observation would not be appropriate for this patient that had a malignancy diagnosed. Evaluation of a patient with cervical adenopathy is summarized in Figure II-23.

II-24. **The answer is E.** *(Chap. 74)* In lung cancer, clinical outcome is related to the stage at diagnosis; hence, it is generally assumed that early detection of occult tumors will lead to improved survival. Initiated in 1993, participants in the PLCO lung cancer screening trial received annual chest x-ray (CXR) screening for 4 years, whereas participants in the usual care group received no interventions other than their customary medical care. Through 13 years of follow-up, cumulative lung cancer incidence rates (20.1 vs 19.2 per 10,000 person-years; rate ratio [RR], 1.05; 95% confidence interval [CI], 0.98–1.12) and lung cancer mortality (n = 1213 vs n = 1230) were identical between the two groups. These data corroborate previous recommendations *against* CXR screening for lung cancer. The National Lung Screening Trial (NLST) was a randomized study designed to determine whether low-dose CT (LDCT) screening could reduce mortality from lung cancer in high-risk populations compared with standard posterior anterior CXR (Table II-24). High-risk patients were defined as individuals between 55 and 74 years of age, with a ≥30 pack-year history of cigarette smoking; former smokers must have quit within the previous 15 years. The overall rates of lung cancer death were 247 and 309 deaths per 100,000 participants in the LDCT and CXR groups, respectively, representing a 20% reduction in lung cancer mortality in the LDCT-screened population (95% CI, 6.8–26.7%; p = 0.004). Compared with the CXR group, the rate of death in the LDCT group from *any* cause was reduced by 6.7% (95% CI, 1.2–13.6; p = 0.02). The number needed to screen (NNTS) to prevent one lung cancer death was calculated to be 320. First-degree relatives of lung cancer probands have a two- to threefold excess risk of lung cancer and other cancers, many of which are not smoking related. These data suggest that specific genes and/or genetic variants may contribute to susceptibility to lung cancer. However, very few such genes have yet been identified and there is no role for genetic testing in patients worried about risk of lung cancer. There are no evidence to support vitamins or supplements to prevent lung cancer.

TABLE II-24 **Results of National Lung Screening Trial**

	Event Number		Rates of Events per 100,000 Person-Years		RR (95% CI)	
	LDCT (n = 26,772)	CXR (n = 26,732)	LDCT	CXR	RR	p value
Lung cancer mortality	356	443	247	309	0.80 (0.73–0.93)	0.004
All-cause mortality	1877	2000	1303	1395	0.93 (0.86–0.99)	0.02
Mortality not due to lung cancer	1521	1557	1056	1086	0.99 (0.95–1.02)	0.51

Abbreviations: CI, confidence interval; CXR, chest x-ray; LDCT, low-dose computed tomography; RR, rate ratio.

Source: Data from Bach PB et al: Benefits and harms of CT screening for lung cancer: a systematic review. *JAMA* 307:2418, 2012.

II-25. **The answer is B.** *(Chap. 74)* The World Health Organization (WHO) classification system divides epithelial lung cancers into four major cell types: small-cell lung cancer (SCLC), adenocarcinoma, squamous cell carcinoma, and large-cell carcinoma; the latter three types are collectively known as non–small-cell carcinomas (NSCLCs). In addition to distinguishing between small-cell lung cancer and non–small-cell lung cancer because these tumors have quite different natural histories and therapeutic approaches, it is necessary to classify if NSCLC is squamous or nonsquamous because of the recognition that some active chemotherapy agents perform quite differently in squamous carcinomas versus adenocarcinomas and the different recommendations for molecular testing (Figure II-25). Therefore, waiting for pathology results is critical. *EGFR* mutations are amenable to targeted treatments such as erlotinib or cetuximab. *KRAS* mutations, while common in NSCLC, do not currently have therapeutic targets in NSCLC. Additional symptomatic measures, like thoracentesis, can help relieve some of the symptoms the patient is acutely experiencing while awaiting pathology results. Malignant pleural effusion would also classify this as stage IV disease and surgery would not be the primary therapy.

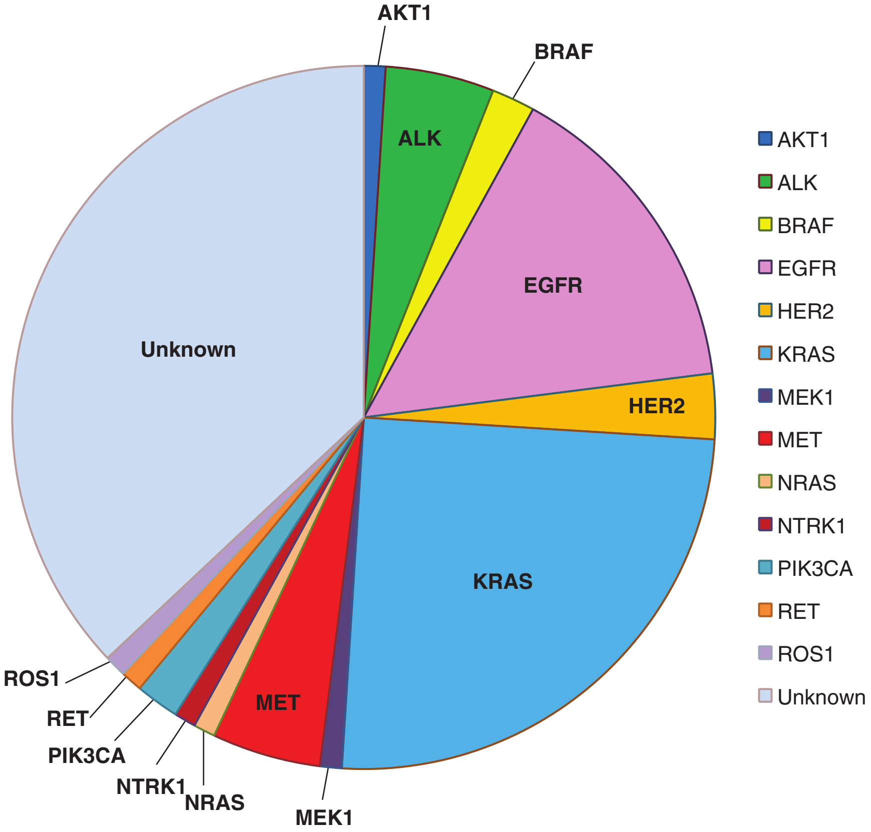


FIGURE II-25 Driver mutations in lung adenocarcinomas.

II-26. **The answer is A.** *(Chap. 74)* Small cell lung cancer (SCLC) may be distinguished from non–small cell lung cancer (NSCLC) by the presence of neuroendocrine markers including CD56, neural cell adhesion molecule, synaptophysin, and chromogranin. In SCLC patients, current staging recommendations include a positron emission tomography-CT scan and MRI of the brain (positive in 10% of asymptomatic patients). Cardiac tamponade, malignant pleural effusion, and bilateral pulmonary parenchymal involvement generally qualify disease as extensive disease, because the involved organs cannot be encompassed safely or effectively within a single radiation therapy port. Sixty to 70% of patients are diagnosed with extensive disease at presentation. Surgery does not have a high cure rate in SCLC. Instead, chemotherapy and radiation play a major role in treatment.

II-27. **The answer is E.** *(Chap. 74)* The evaluation and treatment of solitary pulmonary nodules are important to understand. This patient has a long smoking history with a new nodule that was not apparent by chest x-ray 3 years previously. This should be assumed to be a malignant nodule, and definitive diagnosis and treatment should be attempted. The option for diagnostic and staging procedures include positron emission tomography (PET)-CT scan, bronchoscopic biopsy, percutaneous needle biopsy, or surgical biopsy with concomitant resection if positive. PET/CT would not be high yield in this patient given the small size of the primary lesion (<1 cm) and the lack of enlarged mediastinal lymph nodes. Likewise, bronchoscopy would not provide a good yield because the lesion is very peripheral in origin, and a negative biopsy for malignancy would not be definitive. Appropriate approaches would be to either perform a percutaneous needle biopsy with CT guidance or perform a surgical biopsy with definitive resection if positive. Because this patient has preserved lung function, surgical biopsy and resection are good treatment options for this patient. A repeat CT scan assessing for interval growth would only be appropriate if the patient declined further workup at this time. Referral for treatment with radiation therapy is not appropriate in the absence of tissue diagnosis of malignancy, and surgical resection is the preferred primary treatment because the patient has no contraindications to surgical intervention.

II-28. **The answer is E.** *(Chap. 74)* Pancoast syndrome results from apical extension of a lung mass into the brachial plexus with frequent involvement of the eighth cervical and first and second thoracic nerves. As the tumor continues to grow, it will also involve the sympathetic ganglia of the thoracic chain. The clinical manifestations of a Pancoast tumor include shoulder and arm pain and Horner syndrome (ipsilateral ptosis, miosis, and anhidrosis). Often, the shoulder and arm pain present several months prior to diagnosis. The most common cause of Pancoast syndrome is an apical lung tumor, usually non–small-cell lung cancer. Other causes include mesothelioma and infection, among others. Although midbrain lesions can cause Horner syndrome, other cranial nerve abnormalities would be expected. Enlarged mediastinal lymph nodes and masses in the middle mediastinum can occlude the superior vena cava, leading to superior vena cava syndrome. Individuals with superior vena cava syndrome typically present with dyspnea and have evidence of facial and upper extremity swelling. Eaton-Lambert myasthenic syndrome is caused by antibodies to voltage-gated calcium channels and is characterized by generalized weakness of muscles that increases with repetitive nerve stimulation. Cervical ribs can cause thoracic outlet syndrome by compression of nerves or vasculature as they exit the chest. This typically presents with ischemic symptoms to the affected limb, but intrinsic wasting of the muscles of the hand can be seen due to neurologic compromise.

II-29. **The answer is C.** *(Chap. 74)* Mutations of the epidermal growth factor receptor (EGFR) have recently been recognized as important mutations that affect the response of non–small-cell lung cancers to treatment with EGFR tyrosine kinase inhibitors. Initial studies of erlotinib in all patients with advanced non–small-cell lung cancer failed to show a treatment benefit; however, when only those patients with EGFR mutations were considered, treatment with anti-EGFR therapy improved progression-free and overall survival. Patients who are more likely to have EGFR mutations are women, nonsmokers, Asians, and patients with adenocarcinoma histopathology. Targeted treatments may be first-line therapy in some patients with EGFR mutation positive tumors.

II-30. **The answer is C.** *(Chap. 75)* Breast cancer risk is increased in women with early menarche, late first full-term pregnancy, and late menopause. These three factors account for 70–80% of the variation in breast cancer frequency in different countries. Moderate alcohol intake also increases the risk of breast cancer by an unknown mechanism. Duration of maternal nursing correlates with substantial risk reduction of breast cancer independent of either parity or age at first full-term pregnancy. Central obesity is both a risk factor for occurrence and recurrence of breast cancer.

II-31. **The answer is C.** *(Chap. 75)* Surveillance guidelines for routine follow-up of breast cancer patients are shown in Table II-31. Mammograms should be continued annually in women with a history of breast cancer. No special follow-up procedures, such as serial circulating tumor biomarkers or systemic radiographic/scintigraphic imaging, are indicated in an

TABLE II-31 Follow-up of Early Breast Cancer after Diagnosis and Initial Treatment

	Frequency of Examination		
	1–3 Years	3–5 Years	5+ Years
History and physical examination	Every 3–6 mo	Every 6–12 mo	Yearly
Breast self-examination	Monthly	Monthly	Monthly
Mammogram[a]	Yearly	Yearly	Yearly
Gynecologic examination[b]	Yearly	Yearly	Yearly
Other[c]	PRN	PRN	PRN

[a] Breast MRI is not currently recommended as part of routine screening unless in the setting of a known genetic predisposition or other higher-risk condition.

[b] Yearly gynecologic examinations are recommended, particularly for those on tamoxifen who have an intact uterus.

[c] Tumor marker studies, complete blood count, automated chemistry studies, chest and skeletal x-rays, ultrasound, and radionuclide, CT, and positron emission tomographic scans are not recommended in asymptomatic patients. Appropriate studies should be obtained for patients with signs or symptoms of recurrence only.

Source: Data from Recommended Breast Cancer Surveillance Guidelines. American Society of Clinical Oncology (www.asco.org).

asymptomatic patient with no physical findings of recurrence. Although randomized trials have demonstrated slightly higher incidence of detection of metastases with lead times of 3–12 months by screening asymptomatic patients compared with no special follow-up, there is no evidence of improved overall survival. If anything, one of these studies suggested a worse quality of life due to higher anxiety levels associated with the testing, and toxicities associated with earlier treatment in patients who were otherwise doing well at that time. Serial echocardiography should be performed every 3 months for patients on adjuvant trastuzumab, but not after it is discontinued. Likewise, there is no role for serial monitoring for long-term, life-threatening toxicities associated with chemotherapy, such as myelodysplastic syndromes or congestive heart failure, since these are quite uncommon and likely to cause obvious symptoms requiring proper evaluation if they occur.

II-32. **The answer is A.** *(Chap. 76)* A strong family history of colon cancer should prompt consideration for hereditary nonpolyposis colon cancer (HNPCC), particularly if diffuse polyposis is *not* noted on colonoscopy. HNPCC is characterized by (1) three or more relatives with histologically proven colorectal cancer, one of whom is a first-degree relative and of the other two, at least one had the diagnosis before age 50, and (2) colorectal cancer in at least two generations. The disease is an autosomal dominant trait and is associated with other tumors, including in the endometrium and ovary. The proximal colon is most frequently involved, and cancer occurs with a median age of 50 years, 15 years earlier than in sporadic colon cancer. Patients with HNPCC are recommended to receive biennial colonoscopy and pelvic ultrasound beginning at age 25. Innumerable polyps suggest the presence of one of the autosomal dominant polyposis syndromes, many of which carry a high malignant potential. These include familial adenomatous polyposis, Gardner syndrome (associated with osteomas, fibromas, epidermoid cysts), or Turcot syndrome (associated with brain cancer). Peutz-Jeghers syndrome is associated with mucocutaneous pigmentation and hamartomas. Tumors may develop in the ovary, breast, pancreas, and endometrium; however, malignant colon cancers are not common. Ulcerative colitis is strongly associated with development of colon cancer, but it is unusual for colon cancer to be the presenting finding in ulcerative colitis. Patients are generally symptomatic from their inflammatory bowel disease long before cancer risk develops.

II-33. **The answer is E.** *(Chap. 76)* Esophageal cancer has a high mortality rate as most patients do not present until advanced disease is present. The typical presenting symptoms of esophageal cancer are dysphagia and significant weight loss. Dysphagia is typically fairly rapidly progressive over a period of weeks to months. Dysphagia initially is only to solid foods but progresses to include semisolids and liquids. For dysphagia to occur, an estimated 60% of the esophageal lumen must be occluded. Weight loss occurs due to decreased oral intake in addition to the cachexia that is common with cancer. Associated symptoms may include pain with swallowing that can radiate to the back, regurgitation or vomiting of undigested food, and aspiration pneumonia. The two major cell types of esophageal cancer in the United States are adenocarcinoma and squamous cell carcinoma, which have different risk factors. Individuals with squamous cell carcinomas typically have a history of both tobacco and alcohol abuse, whereas those with adenocarcinoma more often have a history of long-standing gastroesophageal reflux disease and Barrett esophagitis. Among those with a history of alcohol and tobacco abuse, there is an increased risk with increased intake, and interestingly, risk is more associated with whiskey drinking when compared with wine or beer. Other risk factors for squamous cell carcinoma of the esophagus include ingestion of nitrites, smoked opiates, fungal toxins in pickled vegetables, and physical insults that include long-standing ingestion of very hot tea or lye.

II-34. **The answer is C.** *(Chap. 76)* A variety of causative factors have been implicated in the development of squamous cell cancers of the esophagus. In the United States, the etiology of such cancers is primarily related to excess alcohol consumption and/or cigarette smoking. The relative risk increases with the amount of tobacco smoked or alcohol consumed, with these factors acting synergistically. Squamous cell esophageal carcinoma has also been associated with the ingestion of nitrates, smoked opiates, and fungal toxins in pickled vegetables, as well as mucosal damage caused by such physical insults as long-term exposure to extremely hot tea, the ingestion of lye, radiation-induced strictures, and chronic achalasia. The presence of an esophageal web in association with glossitis and iron deficiency (i.e., Plummer-Vinson or Paterson-Kelly syndrome) and congenital hyperkeratosis and pitting of the palms and soles (i.e., tylosis palmaris et plantaris) have each been linked with squamous cell esophageal cancer, as have dietary deficiencies of molybdenum, zinc, selenium, and vitamin A. Several strong etiologic associations have been observed to account for the development of adenocarcinoma of the esophagus. Such tumors arise in the distal esophagus in association with chronic gastric reflux, often in the presence of Barrett esophagus (replacement of the normal squamous epithelium of the distal esophagus by columnar mucosa), which occurs more commonly in obese individuals. Adenocarcinomas arise within dysplastic columnar epithelium in the distal esophagus. Cigarette smoking is associated with the development of adenocarcinoma of the esophagus as well.

II-35. **The answer is A.** *(Chap. 77)* The most effective class of chemopreventive agents is aspirin and other nonsteroidal anti-inflammatory drugs, which are thought to suppress cell proliferation by inhibiting prostaglandin synthesis. Regular aspirin use reduces the risk of colon adenomas and carcinomas as well as death from large-bowel cancer; such use also appears to diminish the likelihood for developing additional premalignant adenomas following successful treatment for a prior colon carcinoma. This effect of aspirin on colon carcinogenesis increases with the duration and dosage of drug use. While *Streptococcus bovis* infection has been associated with colon cancer, it is not clear that antibiotics play a role in reducing that risk. There is considerable debate regarding statins, but statins have not been found to decrease the incidence or mortality from colon cancer. Antioxidant vitamins such as ascorbic acid, tocopherols, and beta-carotene are ineffective at reducing the incidence of subsequent adenomas in patients who have undergone the removal of a colon adenoma. Emerging data linking adequate plasma levels of vitamin D with reduced risk of adenomatous polyps and colorectal cancer appear promising. The value of vitamin D as a form of chemoprevention is under study.

II-36. **The answer is D.** *(Chap. 77)* The development of anal cancer is associated with infection by human papillomavirus, the same organism etiologically linked to cervical cancer and some oropharyngeal cancers. The virus is sexually transmitted. The infection may lead to anal warts (condyloma acuminata), which may progress to anal intraepithelial neoplasia and on to squamous cell carcinoma. The risk for anal cancer is increased among males who have sex with males, presumably related to anal intercourse. Anal cancer risk is increased in both men and women with AIDS, possibly because their immunosuppressed state permits more severe papillomavirus infection. Vaccination against human papilloma viruses appears to reduce the eventual risk for anal cancer. For unknown reasons, individuals who develop endocarditis or septicemia from *Streptococcus bovis* bacterium have a high incidence of occult colorectal tumors, not anal cancers, and, possibly, upper gastrointestinal cancers as well. The main risk factor for liver cancer is cirrhosis and associated chronic liver damage caused by inflammation and fibrosis of any etiology, which explains why 80% of hepatocellular cancer cases worldwide result from chronic hepatitis B virus or hepatitis C virus infection. The risk for developing gastric cancer is thought to be sixfold higher in people infected with *Helicobacter pylori*.

II-37. **The answer is D.** *(Chap. 78)* Liver cancer is the sixth most common cancer worldwide, the second leading cause of cancer-related deaths, and one of the few neoplasms whose incidence and mortality rates have been steadily increasing (Figure II-37). While the proportion of patients with prostate cancer being diagnosed with metastatic disease has increased recently, mortality is not increasing.

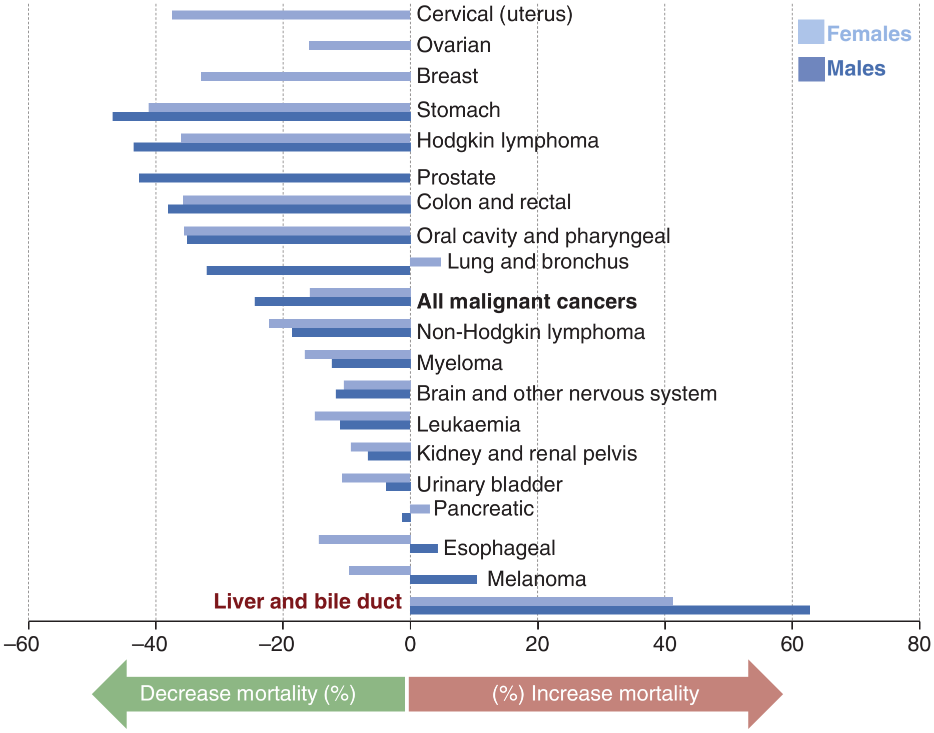
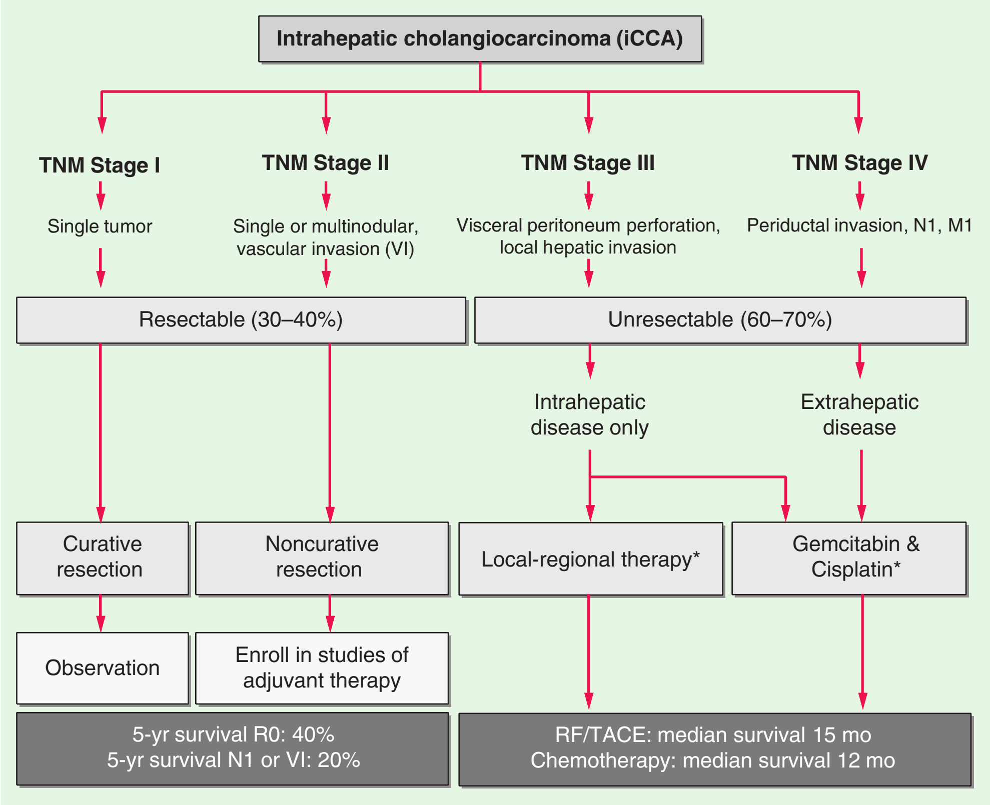


FIGURE II-37 Mortality trends of patients with different malignancies in the United States between 1990 and 2009. Changes in cancer mortality across tumor types in the United States. Liver and bile duct cancer rank first in terms of increase mortality for both men and women. (Reproduced with permission from Llovet JM et al: Advances in targeted therapies for hepatocellular carcinoma in the genomic era. *Nat Rev Clin Oncol* 12:408, 2015.)

II-38. **The answer is C.** *(Chap. 78)* Overall, most of the treatments endorsed have a modest level of evidence; thus, guidelines are providing physicians with recommendations as standards of practice rather than standards of care supported by robust evidence-based data (Figure II-38). Surgical resection represents the sole curative treatment option in 30–40% of patients with a 5-year survival of 30%. The largest systematic review including ~4500 intrahepatic cholangiocarcinoma patients undergoing resection reported a median survival of 28 months. In noncirrhotic individuals, the best candidates for resection are patients at TNM stage I-II, whereas in patients with cirrhosis liver function should be assessed for hepatocellular carcinoma. The main predictors of recurrence (~50–60% at 3 years) and survival are identified at the pathological examination, including presence of vascular invasion, lymph node metastases, and poor differentiation. There is no established adjuvant therapy. Liver transplantation remains controversial, and few studies have reported good outcomes for single tumors ≤2 cm.


Intrahepatic cholangiocarcinoma (iCCA)
TNM Stage I
TNM Stage II
TNM Stage III
TNM Stage IV
Single tumor
Single or multinodular, vascular invasion (VI)
Visceral peritoneum perforation, local hepatic invasion
Periductal invasion, N1, M1
Resectable (30–40%)
Unresectable (60–70%)
Intrahepatic disease only
Extrahepatic disease
Curative resection
Noncurative resection
Local-regional therapy*
Gemcitabin & Cisplatin*
Observation
Enroll in studies of adjuvant therapy
5-yr survival R0: 40%
5-yr survival N1 or VI: 20%
RF/TACE: median survival 15 mo
Chemotherapy: median survival 12 mo

** Treatments used as standard of practice. Not enough evidence for standard of care*

FIGURE II-38 Staging and treatment schedule for intrahepatic cholangiocarcinoma (iCCA) proposed by the International Liver Cancer Association. *Abbreviation:* RF/TACE, radio frequency/trancatheter arterial chemoembolization. (Reproduced with permission from Bridgewater J et al: Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. *J Hepatol* 60:1268, 2014.)

II-39. **The answer is E.** *(Chap. 78)* Hepatomegaly is the most common physical sign in patients with hepatocellular carcinoma (HCC), occurring in 50–90% of the patients. Abdominal bruits are noted in 6–25%, and ascites occurs in 30–60% of patients. α-Fetoprotein (AFP) is a serum tumor marker for HCC; however, it is only increased in approximately one-half of U.S. patients. Rising AFP in a patient at risk of HCC may be a marker of development of disease, and, in some cases, serial measurement of AFP may be used as a marker of response to therapy. An ultrasound examination of the liver is an excellent screening tool. The two characteristic vascular abnormalities are hypervascularity of the tumor mass (neovascularization or abnormal tumor-feeding arterial vessels) and thrombosis by tumor invasion of otherwise normal portal veins. To determine tumor size and extent and the presence of portal vein invasion accurately, a helical/triphasic CT scan of the abdomen and pelvis, with fast-contrast bolus technique, should be performed to detect the vascular lesions typical of HCC. Portal vein invasion is normally detected as an obstruction and expansion of the vessel. An MRI can also provide detailed information, especially with the newer contrast agents. A prospective comparison of triphasic CT, gadolinium-enhanced MRI, ultrasound, and fluorodeoxyglucose (FDG)-positron emission tomography (PET) showed similar results for CT, MRI, and ultrasound; PET imaging appears to be positive in only a subset of HCC patients. MRI is better able to distinguish dysplastic or regenerative nodules from HCC. Imaging criteria have been developed for HCC that do not require biopsy proof, as they have >90% specificity. The criteria include nodules >1 cm with arterial enhancement and portal venous washout and, for small tumors, specified growth rates on two scans performed less than 6 months apart (Organ Procurement and Transplant Network). Nevertheless, explant pathology after liver transplant for HCC has shown that approximately 20% of patients diagnosed without biopsy did not actually have a tumor.

II-40. **The answer is B.** *(Chap. 79)* Hereditary factors may account for 10–16% of all pancreatic cancers. It is very important to recognize these factors for determining risk for family

TABLE II-40 Germline Mutations, Their Familial Cancer Syndrome, and Fold Risk of Pancreatic Cancer

Germline Mutation	Familial Cancer Syndrome	Estimated Increased Risk (fold) of Pancreatic Cancer
BRCA2[a]	Familial breast/ovarian cancer	3.5–10
PALB2 (partner and localizer of BRCA2)	Familial breast cancer and others	Approximately sixfold
p16/CDKN2A	Familial atypical multiple mole melanoma (FAMMM)	13–38
STKII (LKB1)	Peutz-Jeghers syndrome	132
PRSS1 or SPIN11[b]	Hereditary (familial) pancreatitis	53
ATM	Ataxia-telangiectasia	Not yet established
MLH1, MSH2, MSH6, PMS2	Heredity nonpolyposis colorectal syndrome or Lynch syndrome[c]	9–30

[a] Particularly common in individuals with Ashkenazi Jewish heritage.
[b] Forty percent chance of pancreatic cancer by the age of 70.
[c] Very important because this is associated with microsatellite instability, which is a marker for response to an anti-PD-1/PD-L1 agent.

members of the patient affected with pancreatic cancer. The identification of any of these germline mutations can lead to specific and effective new therapeutics for patients with these abnormalities in their tumors. Table II-40 identifies the various germline mutations along with their familial cancer syndromes where an increased risk for pancreatic cancer is known. Other germline mutations are under study to determine their increased risk of pancreatic cancer including *CDK4, FANCC, PALLD, APC, ATM, BMPR1A, BRCA1, EPCAM, MEN1, MLH1, MSH2, MSH6, NF1, PMS2, SMAD4, TP53, TSC1, TSC2,* and *VHL*. *CFTR* is the gene associated with cystic fibrosis.

II-41. **The answer is B.** *(Chap. 79)* Dual-phase, contrast-enhanced spiral CT is the imaging modality of choice to visualize suspected pancreatic masses. In addition to imaging the pancreas, it also provides accurate visualization of surrounding viscera, vessels, and lymph nodes. In most cases, this study can determine surgical resectability. There is no advantage of MRI over CT in predicting tumor resectability, but selected cases may benefit from MRI to characterize the nature of small indeterminate liver lesions and to evaluate the cause of biliary dilatation when no obvious mass is seen on CT. Preoperative confirmation of malignancy is not always necessary in patients with radiologic appearances consistent with operable pancreatic cancer. Endoscopic ultrasound-guided needle biopsy is the most effective technique to evaluate the mass for malignancy. It has an accuracy of approximately 90% and has a smaller risk of intraperitoneal dissemination compared with CT-guided percutaneous biopsy. Endoscopic retrograde cholangiopancreatography is a useful method for obtaining ductal brushings, but the diagnostic value of pancreatic juice sampling is only 25–30%. CA 19-9 is elevated in approximately 70–80% of patients with pancreatic carcinoma but is not recommended as a routine diagnostic or screening test because its sensitivity and specificity are inadequate for accurate diagnosis. Preoperative CA 19-9 levels correlate with tumor stage and prognosis. They are also an indicator of asymptomatic recurrence in patients with completely resected tumors. Fluorodeoxyglucose-positron emission tomography (FDG-PET) should be considered before surgery for detecting distant metastases.

II-42. **The answer is C.** *(Chap. 80)* This patient has a malignant carcinoid tumor with metastatic disease to the lungs manifesting as the carcinoid syndrome. Cardiac manifestations occur initially in 11–40% (mean 26%) of patients with carcinoid syndrome and in 14–41% (mean 30%) at some time in the disease course. The cardiac disease is due to the formation of fibrotic plaques (composed of smooth-muscle cells, myofibroblasts, and elastic tissue) involving the endocardium, primarily on the right side, although lesions on the left side also occur occasionally (mean 11%, range 0–25), especially if a patent foramen ovale exists. The dense fibrous deposits are most commonly on the ventricular aspect of the tricuspid valve and less commonly on the pulmonary valve cusps. They can result in constriction of the valves, and pulmonic stenosis is usually predominant, whereas the tricuspid valve is often fixed open, resulting in regurgitation predominating. In patients with carcinoid heart disease, 90–100% have tricuspid insufficiency, 43–59% have tricuspid stenosis, 50–81% have pulmonary insufficiency, 25–59% have pulmonary stenosis, and 11% (0–25%) left-side lesions. Up to 80% of patients with cardiac lesions develop heart failure. Lesions on the left side are much less extensive, occur in 30% at autopsy, and most frequently affect the mitral valve. Up to 80% of patients with cardiac lesions have evidence of heart failure. At diagnosis in various series, 27–43% of patients are in New York Heart Association class I, 30–40% are in class II, 13–31% are in class III, and 3–12% are in class IV. At present, carcinoid heart disease is reported to be decreasing in frequency and severity, with mean occurrence in 20% of patients and occurrence in as few as 3–4% in some reports. Whether this decrease is due to the widespread use of somatostatin analogues, which control the release of bioactive agents thought involved in mediating the heart disease, is unclear.

II-43. **The answer is D.** *(Chap. 81)* Kidney cancer was called the "internist's tumor" since it was often discovered from classic triad of hematuria, flank pain, and palpable mass or from a paraneoplastic syndrome. A spectrum of paraneoplastic syndromes has been associated with renal cell carcinoma, including erythrocytosis, hypercalcemia, nonmetastatic hepatic dysfunction (Stauffer syndrome), and acquired dysfibrinogenemia. Now most cases are diagnosed as an incidental finding on an abdominal imaging study. Erythrocytosis is noted at presentation in only ~3% of patients. Anemia, a sign of metastatic disease, is more common. Most cases of renal cell carcinoma are sporadic, although familial forms have been reported (Table II-43). One such form is associated with von Hippel-Lindau (VHL) syndrome, an autosomal dominant disorder. Genetic studies identified the *VHL* gene on the short arm of chromosome 3. Approximately 35% of individuals with VHL disease develop clear cell renal cell carcinoma. Other *VHL*-associated neoplasms include retinal hemangioma, hemangioblastoma of the spinal cord and cerebellum, pheochromocytoma, and neuroendocrine tumors and cysts.

TABLE II-43 Hereditary Renal Cell Tumors

Syndrome	Chromosome(s)	Gene	Protein	Kidney Tumor Type	Additional Findings
von Hippel-Lindau syndrome	3p25	*VHL*	von Hippel-Lindau protein	Clear cell	Hemangioblastoma of the retina and central nervous system; pheochromocytoma; pancreatic and renal cysts; neuroendocrine tumors
Hereditary papillary RCC	7p31	*MET*	MET	Papillary (type I)	
Hereditary leiomyomatosis and RCC	1q42	*FH*	Fumarate hydratase	Papillary (non–type I)	Leiomyoma; uterine leiomyoma/leiomyosarcoma
Birt-Hogg-Dubé syndrome	17p11	*FLCN*	Folliculin	Chromophobe, oncocytoma	Facial fibrofolliculoma; pulmonary cysts
Tuberous sclerosis	9q34 16p13	*TSC1* *TSC2*	Hamartin Tuberin	Angiomyolipomas; lymphangioleiomyomatosis; rare RCC with variety of histologic appearances	Angiofibroma, subungual fibroma; cardiac rhabdomyoma; adenomatous small intestine polyps; pulmonary and renal cysts; cortical tuber; subependymal giant cell astrocytomas
Constitutional chromosome 3 translocations	3p13-14	Unknown	Unknown	Clear cell	

Abbreviation: RCC, renal cell carcinoma.

II-44. **The answer is A.** *(Chap. 81)* Metastatic renal cell carcinoma is refractory to cytotoxic chemotherapy. Cytokine therapy with interleukin-2 or interferon-α produces regression in 10–15% of patients. IL-2 produces durable complete remission in a small proportion of cases. In general, cytokine therapy is considered unsatisfactory for most patients due to high levels of toxicity and the unpredictability of response. Cytoreductive nephrectomy before systemic treatment improves survival for carefully selected patients with stage IV tumors. A randomized phase III trial comparing sunitinib to interferon-α showed superior efficacy for sunitinib with an acceptable safety profile. This trial resulted in a change in the standard first-line treatment from interferon to sunitinib. These were followed by eight new systemic agents for metastatic renal cell carcinoma: pazopanib, axitinib, cabozantinib, and lenvatinib, also tyrosine kinase inhibitors; the antiangiogenic bevacizumab that inhibits the vascular endothelial growth factor ligand; the mammalian target of rapamycin inhibitors temsirolimus and everolimus; and nivolumab, which inhibits PD-1. Although the improvements in 5-year renal cancer survival rates over the past decades (50% in the mid-1970s, 57% in the late 1980s, and 74% for 2005–2012) can largely be attributed to widespread imaging leading to earlier discovery of tumors, the new agents are likely playing a part as well.

II-45. **The answer is E.** *(Chap. 82)* This patient should be evaluated for bladder cancer. Males are affected with bladder cancer four times more frequently than females. Patients with Cowden disease (*PTEN* mutations with hamartomas) or retinoblastoma (*RB1* mutations) are at increased risk for developing bladder cancer. Cytology is successful in identifying cancer in only 50% of individuals with high-grade bladder cancers. In addition to urine cytology, radiographic evaluation of the kidneys and upper urinary tract by CT urogram should be performed. Urothelial carcinoma, formerly referred to as *transitional cell carcinoma*, is the most common urinary tract cancer histology and is observed in ~90% of cases. Squamous, glandular, micropapillary, plasmacytoid, sarcomatoid, and other variant features can often be found in portions of urothelial carcinoma tumors; however, pure variant histologies are rare. The presence of some variant histologies including micropapillary and plasmacytoid has been associated with worse surgical outcomes compared with urothelial carcinoma. Nonurothelial variant histologies including squamous cell carcinoma, adenocarcinoma, small-cell carcinoma, and carcinosarcoma collectively account for ≤10% of urinary tract tumors. For nonmuscular invasive bladder cancer (NMIBC), removal of all visible tumors by transurethral resection of the bladder tumor (TURBT) in the operating room is considered the mainstay of surgical treatment. For patients with low-risk disease meta-analyses have demonstrated a 12% reduction in early relapses when a single chemotherapy treatment of mitomycin C, epirubicin, or gemcitabine was instilled directly into the bladder (intravesical therapy) within 24 hours of the TURBT. For patients with intermediate- or high-risk tumors, weekly intravesical instillations for 6 consecutive weeks of the attenuated mycobacterium strain known as Bacillus Calmette-Guérin (BCG) reduce the risk of recurrence at 12 months from 56 to 29%.

II-46. **The answer is D.** *(Chap. 83)* Alpha-adrenergic receptor antagonists are thought to treat the dynamic aspect of benign prostatic hypertrophy (BPH) by reducing sympathetic tone of the bladder outlet, decreasing resistance and improving urinary flow. 5α-reductase inhibitors (5ARIs) are thought to treat the static aspect of BPH by reducing prostate volume and having a similar, albeit delayed effect. They have also proven to be beneficial in the prevention of BPH progression, as measured by prostate volume, the risk of developing acute urinary retention, and the risk of having BPH-related surgery. The use of an α-adrenergic receptor antagonist and a 5ARI as combination therapy seeks to provide symptomatic relief while preventing progression of BPH. Another class of medications that has shown improvement in lower urinary tract symptoms (LUTS) secondary to BPH is phosphodiesterase-5 (PDE5) inhibitors, used currently in the treatment of erectile dysfunction, which prolong the vasodilatory effect of nitrous oxide. All four of the PDE5 inhibitors available in the United States, sildenafil, vardenafil, tadalafil, and avanafil, appear to be effective in the treatment of LUTS secondary to BPH. The use of PDE5 inhibitors is not without controversy, however, given the fact that short-active phosphodiesterase inhibitors such as sildenafil need to be dosed separately from alpha blockers such as tamsulosin because of potential hypotensive effects.

II-47. **The answer is D.** *(Chap. 83)* No agent is currently approved for the prevention of prostate cancer. The results from several large double-blind, randomized chemoprevention trials have established 5α-reductase inhibitors (5ARIs) as the predominant therapy to reduce the future risk of a prostate cancer diagnosis. The Prostate Cancer Prevention Trial (PCPT), in which men aged >55 years received placebo or the 5ARI finasteride, which inhibits the type 1 isoform, showed a 25% (95% confidence interval 19–31%) reduction in prostate cancer incidence from 24% with placebo to 18% with finasteride. In the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial, a reduction in incidence from 25% with placebo to 20% with dutasteride was found (p = 0.001). Dutasteride inhibits both the type 1 and type 2 5ARI isoforms. While both studies met their end point, there was concern that most of the cancers that were prevented were low risk and that there was a slightly higher rate of clinically significant cancers (those with higher Gleason scores) in the treatment arm. Neither drug is approved for prostate cancer prevention. In comparison, the Selenium and Vitamin E Cancer Prevention Trial (SELECT), which enrolled African American men aged ≥50 years and others aged ≥55 years, showed no difference in cancer incidence in patients receiving vitamin E (4.6%) or selenium (4.9%) alone or in combination (4.6%) relative to placebo (4.4%). A similar lack of benefit for vitamin E, vitamin C, and selenium was seen in the Physicians Health Study II. The prevalence of autopsy-detected cancers is similar around the world, whereas the incidence of clinical disease varies. Thus, environmental and dietary factors may play a role in prostate cancer growth and progression. High consumption of dietary fats, such as α-linoleic acid or polycyclic aromatic hydrocarbons that form when red meats are cooked, is believed to increase risk. Protective factors include consumption of the isoflavonoid genistein (which inhibits 5α-reductase), cruciferous vegetables with isothiocyanate sulforaphane, lycopene found in tomatoes, and inhibitors of cholesterol biosynthesis (e.g., statin drugs).

II-48. **The answer is B.** *(Chap. 83)* Prostate-specific antigen (PSA) (kallikrein-related peptidase 3; *KLK3*) is a kallikrein-related serine protease that causes liquefaction of seminal coagulum. It is produced by both nonmalignant and malignant epithelial cells and, as such, is prostate specific, not prostate cancer specific. Serum levels may also increase from prostatitis and BPH. Serum levels are not significantly affected by direct rectal examination, but the performance of a cystoscopy or prostate biopsy can increase PSA levels up to 10-fold for 8–10 weeks. Immunohistochemical staining for PSA can be used to establish a prostate cancer diagnosis. As of 2017, the U.S. Preventive Services Task Force (USPSTF) has issued a draft of a revised recommendation with a grade of "C" for PSA-based prostate cancer screening for men aged 55–69. They recommend shared decision-making for men aged 55–69 and do not recommend screening for men aged ≥70; this is now roughly in agreement with the 2013 American Urological Association (AUA) guideline. The USPSTF notes that the increased use of active surveillance (observation with selective delayed treatment) for low-risk prostate cancer has reduced the risks of screening. Patients with symptomatic prostatitis should have a course of antibiotics before biopsy. However, the routine use of antibiotics in an asymptomatic man with an elevated PSA level is strongly discouraged.

II-49. **The answer is E.** *(Chap. 83)* Transrectal ultrasound-guided biopsy is recommended for men with an abnormal digital rectal examination. Carcinomas are characteristically hard, nodular, and irregular, whereas induration may also be due to benign prostatic hypertrophy or calculi. Overall, 20–25% of men with an abnormal digital rectal examination have cancer. A diagnosis of cancer is established by an image-guided needle biopsy. Direct visualization by transrectal ultrasound or MRI ensures that all areas of the gland are sampled. Contemporary schemas advise an extended pattern 12-core biopsy that includes sampling from the peripheral zone as well as a lesion-directed palpable nodule or suspicious image-guided sampling. Men with an abnormal prostate-specific antigen level and negative biopsy are advised to undergo a repeat biopsy. When prostate cancer is diagnosed, a measure of histologic aggressiveness is assigned using the Gleason grading system, in which the dominant and secondary glandular histologic patterns are scored from 1 (well differentiated) to 5 (undifferentiated) and summed to give a total score of 2–10 for each tumor. The most poorly differentiated area of tumor (i.e., the area with the highest histologic grade) often determines biologic behavior. The presence or absence of perineural invasion and extracapsular spread is also recorded.

II-50. **The answer is E.** *(Chap. 84)* Because most patients with testicular germ cell tumor (GCT) will experience long-term survival, survivorship care is important. Since many of these patients will be followed by primary care physicians, an understanding of the physical, psychological, and social late effects is important. Late effects are defined as health problems that occur months or years after a disease is diagnosed or after treatment has ended. Late effects may be related to the underlying cancer or to the treatment the patient received. In long-term survivors of testicular GCT, increased cardiovascular risk and increased secondary malignancies have been reported. Patients treated with cisplatin-based chemotherapy have an increased risk of hypertension, hyperlipidemia, metabolic syndrome, and cardiovascular events. Patients treated with high cumulative doses of etoposide (such as patients who receive standard chemotherapy, relapse, and then receive salvage high dose chemotherapy) may experience up to a 1–2% risk of developing acute myelogenous leukemia, typically 2–3 years after completing therapy and associated with an 11q23 translocation. Patients treated with radiation therapy, cisplatin-based chemotherapy, or both have an increased risk of developing secondary solid malignancies.

II-51. **The answer is E.** *(Chap. 84)* Pure seminomas have the best survival of all forms of testicular cancer and represent approximately 50% of all germ cell tumors. The median age of presentation is the fourth decade of life, and approximately 80% of individuals present with stage I disease, indicating any disease limited to the testis no matter the size at initial presentation. All men presenting with a testicular mass should be referred for radical inguinal orchiectomy as this approach mirrors the embryonic development of the testis and does not breach anatomic barriers to allow for other pathways of spread. In the staging workup of testicular cancers, men should undergo CT imaging of the chest, abdomen, and pelvis as well as measurement of the serum tumor markers α-fetoprotein (AFP) and β-human chorionic gonadotropin (β-hCG), in addition to lactate dehydrogenase (LDH) levels. These tumor markers assist with both diagnosis and prognosis in testicular cancer and help with determining the appropriate post-orchiectomy treatment. In pure seminomas, AFP levels should not be elevated. If the AFP level is elevated, this indicates an occult nonseminomatous component, which may require more aggressive initial treatment with either retroperitoneal lymph node dissection or adjuvant chemotherapy depending on local surgical expertise and preference of the patient and treating physician. β-hCG levels may be elevated in pure seminomas, although this too is infrequent in men without advanced disease. LDH levels are less specific, but are increased in up to 80% of patients with advanced seminoma. After resection, the tumor markers should return to normal values within their expected half-lives following first-order kinetics. The half-life of β-hCG is 24–36 hours, and that of AFP is 5–7 days. In stage I seminoma, survival is near 100% with either immediate post-orchiectomy radiation or with surveillance alone (option E). Given the concern about secondary malignancy due to radiation exposure, many providers choose watchful waiting with surveillance alone in men who are compliant with follow-up. However, approximately 15% of patients will experience relapse, and 5% of relapses occur after 5 years. Thus, extended follow-up is required. A single dose of carboplatin has been investigated as an alternative to radiation therapy, but long-term outcomes are as yet unknown.

II-52. **The answer is A.** *(Chap. 84)* Ninety percent of persons with nonseminomatous germ cell tumors produce either α-fetoprotein (AFP) or β-human chorionic gonadotropin (β-hCG); in contrast, persons with pure seminomas usually produce neither. These tumor markers are present for some time after surgery; if the presurgical levels are high, 30 days or more may be required before meaningful postsurgical levels can be obtained. The half-lives of AFP and β-hCG are 6 days and 1 day, respectively. After treatment, unequal reduction of β-hCG and AFP may occur, suggesting that the two markers are synthesized by heterogeneous clones of cells within the tumor; thus, both markers should be followed. β-hCG is similar to luteinizing hormone except for its distinctive β subunit.

II-53. **The answer is A.** *(Chap. 85)* Cervical cancer is the second most common and most lethal malignancy in women worldwide likely due to the widespread infection with high-risk

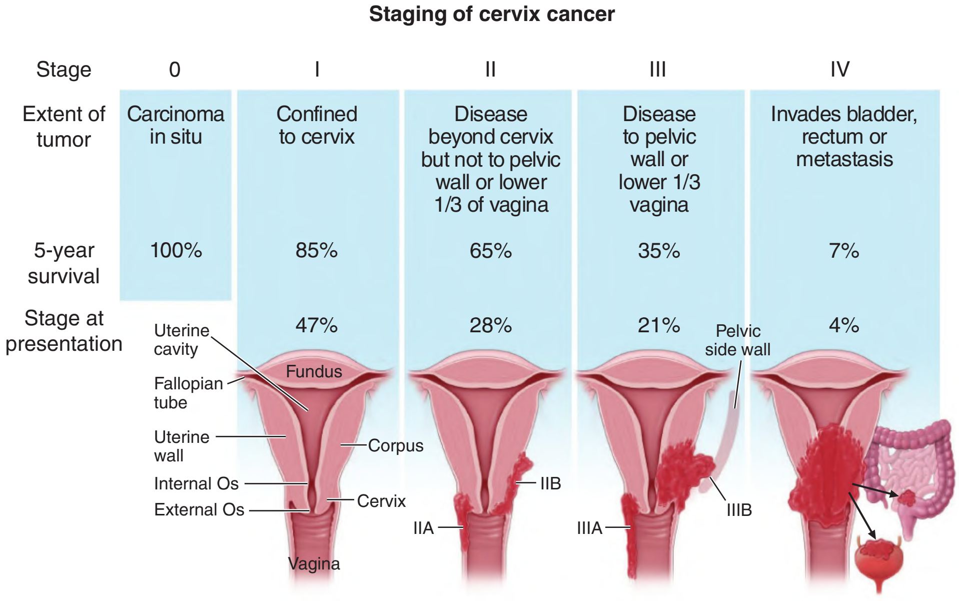

Staging of cervix cancer
Stage
0
I
II
III
IV
Extent of tumor
Carcinoma in situ
Confined to cervix
Disease beyond cervix but not to pelvic wall or lower 1/3 of vagina
Disease to pelvic wall or lower 1/3 vagina
Invades bladder, rectum or metastasis
5-year survival
100%
85%
65%
35%
7%
Stage at presentation
47%
28%
21%
4%
Uterine cavity
Fallopian tube
Uterine wall
Internal Os
External Os
Fundus
Corpus
Cervix
Vagina
IIA
IIB
IIIA
IIIB
Pelvic side wall

FIGURE II-53 Anatomic display of the stages of cervix cancer defined by location, extent of tumor, frequency of presentation, and 5-year survival.

strains of human papillomavirus (HPV) and limited utilization of or access to Pap smear screening in many nations throughout the world. Nearly 500,000 cases of cervical cancer are expected worldwide, with approximately 240,000 deaths annually. Cancer incidence is particularly high in women residing in Central and South America, the Caribbean, and southern and eastern Africa. Mortality rate is disproportionately high in Africa. In the United States, 12,360 women were diagnosed with cervical cancer, and 4020 women died of the disease in 2014. HPV is the primary neoplastic-initiating event in the vast majority of women with invasive cervical cancer. This double-strand DNA virus infects epithelium near the transformation zone of the cervix. More than 60 types of HPV are known, with approximately 20 types having the ability to generate high-grade dysplasia and malignancy. HPV-16 and -18 are the types most frequently associated with high-grade dysplasia and targeted by both U.S. Food and Drug Administration (FDA)-approved vaccines. The large majority of sexually active adults are exposed to HPV, and most women clear the infection without specific intervention. Risk factors for HPV infection and, in particular, dysplasia include a high number of sexual partners, early age of first intercourse, and history of venereal disease. Smoking is a cofactor; heavy smokers have a higher risk of dysplasia with HPV infection. HIV infection, especially when associated with low CD4+ T-cell counts, is associated with a higher rate of high-grade dysplasia and likely a shorter latency period between infection and invasive disease. The administration of highly active antiretroviral therapy reduces the risk of high-grade dysplasia associated with HPV infection. Currently approved vaccines include the recombinant proteins to the late proteins, L1 and L2, of HPV-16 and -18. Vaccination of women before the initiation of sexual activity dramatically reduces the rate of HPV-16 and -18 infection and subsequent dysplasia. Stage I disease, which accounts for almost half of staging at presentation, is defined by carcinoma confined to the cervix and has a >80% 5-year survival (Figure II-53).

II-54. **The answer is E.** *(Chaps. 87 and 190)* Sarcomas are rare (<1% of all malignancies) mesenchymal neoplasms that arise in bone and soft tissues. Trauma or previous injury is rarely involved, but sarcomas can arise in scar tissue resulting from a prior operation, burn, fracture, or foreign body implantation. Chemical carcinogens such as polycyclic hydrocarbons, asbestos, and dioxin may be involved in the pathogenesis. Kaposi sarcoma (KS) in patients with HIV type 1, classic KS, and KS in HIV-negative homosexual men is caused by human herpes virus (HHV)-8. No other sarcomas are associated with viruses. Sarcomas in bone or soft tissues occur in patients who are treated with radiation therapy.

The tumor nearly always arises in the irradiated field. The risk increases with time. Li-Fraumeni syndrome is a familial cancer syndrome in which affected individuals have germline abnormalities of the tumor-suppressor gene *p53* and an increased incidence of soft tissue sarcomas and other malignancies, including breast cancer, osteosarcoma, brain tumor, leukemia, and adrenal carcinoma.

II-55. **The answer is A.** *(Chap. 88)* Carcinoma of unknown primary (CUP) is a biopsy-proven malignancy for which the anatomic site of origin remains unidentified after a focused search. CUP is one of the 10 most frequently diagnosed cancers worldwide, accounting for 3–5% of all cancers. Most tumor markers, including CEA, CA-125, CA 19-9, and CA 15-3, when elevated, are nonspecific and not helpful in determining the primary tumor site. Men who present with adenocarcinoma and predominant osteoblastic metastasis should undergo a prostate-specific antigen (PSA) test. In patients with undifferentiated or poorly differentiated carcinoma (especially with a midline tumor), elevated β-human chorionic gonadotropin (β-hCG) and α-fetoprotein (AFP) levels suggest the possibility of an extragonadal germ cell (testicular) tumor. AFP should also be considered in patients with a potential diagnosis of hepatoma. Adequate tissue obtained preferably by excisional biopsy or core-needle biopsy (instead of only a fine-needle aspiration) is stained with hematoxylin and eosin and subjected to light microscopic examination. On light microscopy, 60–65% of CUP is adenocarcinoma, and 5% is squamous cell carcinoma. The remaining 30–35% is poorly differentiated adenocarcinoma, poorly differentiated carcinoma, or poorly differentiated neoplasm. A small percentage of lesions are diagnosed as neuroendocrine cancers (2%), mixed tumors (adenosquamous or sarcomatoid carcinomas), or undifferentiated neoplasms. The current diagnostic yield with imaging and immunochemistry is ~20–30% for CUP patients. To reduce diagnostic uncertainty, sophisticated molecular analytics have been applied to CUP samples. These include gene expression profiling, messenger RNA (mRNA), microRNA, and epigenetic profiling to classify the CUP cancer. A retrospective study of 200 CUP tumor specimens reported on genomic alterations (GAs) using the hybrid-capture–based FoundationOne assay. The authors reported that a large number of CUP samples (85%) harbored at least one clinically relevant GA with the potential to influence and personalize therapy. The mean number of GAs was 4.2 per tumor, and the most common GAs included *TP53* (55%), *KRAS* (20%), *CDKN2A* (19%), and *ARID1A* (11%). The adenocarcinoma CUP tumors were more frequently driven by GAs in the receptor tyrosine kinase/Ras/mitogen-activated protein kinase signaling pathway than nonadenocarcinoma CUP tumors. The median survival duration of most patients with disseminated CUP is ~6–10 months. Systemic chemotherapy is the primary treatment modality in most patients with disseminated disease, but the careful integration of surgery, radiation therapy, and even periods of observation is important in the overall management of this condition.

II-56. **The answer is E.** *(Chap. 89)* Approximately 30% of patients with solid tumors have granulocytosis (granulocyte count >8000/μL). In about half of patients with granulocytosis and cancer, the granulocytosis has an identifiable nonparaneoplastic etiology (infection, tumor necrosis, glucocorticoid administration, etc.). Some 35% of patients with thrombocytosis (platelet count >400,000/μL) have an underlying diagnosis of cancer. The other patients have proteins in urine and serum that stimulate the growth of bone marrow cells. Tumors and tumor cell lines from patients with lung, ovarian, and bladder cancers have been documented to produce granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, and/or interleukin-6. However, the etiology of granulocytosis has not been characterized in most patients. Patients with granulocytosis are nearly all asymptomatic, and the differential white blood cell count does not have a shift to immature forms of neutrophils. Granulocytosis occurs in 40% of patients with lung and gastrointestinal cancers, 20% of patients with breast cancer, 30% of patients with brain tumors and ovarian cancers, 20% of patients with Hodgkin disease, and 10% of patients with renal cell carcinoma. Patients with advanced-stage disease are more likely to have granulocytosis than are those with early-stage disease. Paraneoplastic granulocytosis does not require treatment. The granulocytosis resolves when the underlying cancer is treated. This patient should receive an evaluation for lung malignancy.

II-57. The answer is A. *(Chap. 91)* Alkylating agents are associated with the highest rates of male and female infertility, which is directly dependent on age, dose, and duration of treatment. The age at treatment is an important determinant of fertility outcome, with prepubertal patients having the highest tolerance. Ovarian failure is age related, and females who resume menses after treatment are still at increased risk for premature menopause. Males generally have reversible azoospermia during lower intensity alkylator chemotherapy, and long-term infertility is associated with doses of cyclophosphamide >9 g/m^2 and with high-intensity therapy, such as that used in hematopoietic stem cell transplantation. Neurocognitive dysfunction has been well described in childhood survivors of acute lymphoblastic leukemia treatment, including those that received intrathecal methotrexate or cytosine arabinoside in conjunction with prophylactic cranial irradiation. Chronic methotrexate toxicity (leukoencephalopathy) develops months or years after treatment and is characterized clinically as progressive loss of cognitive function and focal neurologic signs, which are irreversible, promoted by synchronous or metachronous radiation therapy, and more pronounced at a younger age. Many cancer patients experience intrusive or debilitating concerns about cancer recurrence following successful therapy. In addition, these patients may experience job, insurance, stress, relationship, financial, and sexual difficulties. Oncologists need to ask about and address these issues explicitly with patients and provide appropriate counseling or support systems. Suicidal ideation and suicide have an increased frequency in cancer patients and survivors. Testicles and ovaries in prepubertal patients are less sensitive to radiation damage; spermatogenesis is affected by low doses of radiation, and complete azoospermia occurs at 600–700 cGy. Leydig cell dysfunction, in contrast, occurs at <2000 cGy; hence, endocrine function is lost at much higher radiation doses than spermatogenesis. All former cancer patients should be followed indefinitely. This is most often done by oncologists, but demographic changes suggest that more primary care physicians will need to be trained in the follow-up of treated cancer patients in remission.

II-58. The answer is C. *(Chap. 93)* This patient has iron-deficiency anemia as evidenced by a microcytic anemia combined with the iron studies that show low serum iron, low ferritin, and low percent saturation with an elevated total iron-binding capacity (TIBC). The other conditions to consider in the differential of a microcytic anemia are inflammation, which his iron studies argue against; thalassemia, which his previously normal CBC argue against; or sideroblastic anemia, which would have a normal to high serum iron and TIBC and ferritin. Iron bioavailability is affected by the nature of the foodstuff, with heme iron (e.g., red meat) being most readily absorbed. In the United States, the average iron intake in an adult male is 15 mg/d with 6% absorption; for the average female, the intake is 11 mg/d with 12% absorption. An individual with iron deficiency can increase iron absorption to ~20% of the iron present in a meat-containing diet but only 5–10% of the iron in a vegetarian diet. As a result, one-third of the female population in the United States has virtually no iron stores. Vegetarians are at an additional disadvantage because certain foodstuffs that include phytates and phosphates reduce iron absorption by ~50%. When ionizable iron salts are given together with food, the amount of iron absorbed is reduced. When the percentage of iron absorbed from individual food items is compared with the percentage for an equivalent amount of ferrous salt, iron in vegetables is only about 1/20 as available, egg iron one-eighth, liver iron one-half, and heme iron one-half to two-thirds. Vitamin B_{12} and folate deficiencies cause macrocytic anemia. Desferrioxamine is an iron chelator, which would worsen the anemia.

II-59. The answer is E. *(Chap. 93)* Iron absorbed from the diet or released from stores circulates in the plasma bound to transferrin, the iron transport protein. Transferrin that carries iron exists in two forms: monoferric (one iron atom) or diferric (two iron atoms). The turnover (half-clearance time) of transferrin-bound iron is very rapid, typically 60–90 minutes. Because almost all of the iron transported by transferrin is delivered to the erythroid marrow, the clearance time of transferrin-bound iron from the circulation is affected most by the plasma iron level and the erythroid marrow activity. Ferritin is an iron storage protein, and levels represent an indirect measure of total-body iron stores. Free iron, which is toxic to cells, may also be stored intracellularly bound to hemosiderin. Haptoglobin binds free hemoglobin in the plasma, and low levels are consistent intravascular hemolysis.

Albumin, which binds many serum proteins, does not bind significant amounts of free iron in plasma.

II-60. **The answer is C.** *(Chap. 94)* The smear demonstrates elongated and crescent-shaped red blood cells typical of sickle cell disease. Target cells and a nucleated red blood cell are also seen. The sickle cell syndromes are caused by a mutation in the β-globin gene that changes the sixth amino acid from glutamic acid to valine. HbS ($\alpha_2\beta_2^{6\ \mathrm{Glu}\rightarrow\mathrm{Val}}$) polymerizes reversibly when deoxygenated to form a gelatinous network of fibrous polymers that stiffen the red blood cell membrane, increase viscosity, and cause dehydration due to potassium leakage and calcium influx . These changes also produce the sickle shape. The thalassemia syndromes are inherited disorders of α- or β-globin biosynthesis. Mutations causing thalassemia can affect any step in the pathway of globin gene expression: transcription, processing of the mRNA precursor, translation, and posttranslational metabolism of the β-globin polypeptide chain. The most common forms arise from mutations that derange splicing of the mRNA precursor or prematurely terminate translation of the mRNA. The four classic α thalassemias, most common in Asians, are α thalassemia-2 trait, in which one of the four α-globin loci is deleted; α thalassemia-1 trait, with two deleted loci; HbH disease, with three loci deleted; and hydrops fetalis with Hb Barts, with all four loci deleted. Nondeletion forms of α thalassemia also exist. The two most important acquired hemoglobinopathies are carbon monoxide poisoning and methemoglobinemia. Carbon monoxide has a higher affinity to hemoglobin than does oxygen; it can replace oxygen and diminish O_2 delivery. Chronic elevation of carboxyhemoglobin levels to 10 or 15%, as occurs in smokers, can lead to secondary polycythemia. Carboxyhemoglobin is cherry red in color and masks the development of cyanosis usually associated with poor O_2 delivery to tissues.

II-61. **The answer is C.** *(Chap. 94)* Acute chest syndrome is a distinctive manifestation of sickle cell disease characterized by chest pain, tachypnea, fever, cough, and arterial oxygen desaturation. It can mimic pneumonia, pulmonary emboli, bone marrow infarction and embolism, myocardial ischemia, or in situ lung infarction. Acute chest syndrome is thought to reflect in situ sickling within the lung, producing pain and temporary pulmonary dysfunction. Often it is difficult or impossible to distinguish among other possibilities. Pulmonary infarction and pneumonia are the most frequent underlying or concomitant conditions in patients with this syndrome. Repeated episodes of acute chest pain correlate with reduced survival. Chronic acute or subacute pulmonary crises lead to pulmonary hypertension and cor pulmonale, an increasingly common cause of death as patients survive longer. Considerable controversy exists about the possible role played by free plasma hemoglobin S in scavenging nitric oxide (NO), thus raising pulmonary vascular tone. Trials of sildenafil to restore NO levels were terminated because of adverse effects. Acute chest syndrome is a medical emergency that may require management in an intensive care unit. Hydration should be monitored carefully to avoid the development of pulmonary edema, and oxygen therapy should be administered to avoid hypoxemia. Critical interventions are transfusion to maintain a hematocrit >30% and emergency exchange transfusion if arterial saturation drops to <90%. The most significant advance in the therapy of sickle cell anemia has been the introduction of hydroxyurea as a mainstay of therapy for patients with severe symptoms. Hydroxyurea (10–30 mg/kg per day) increases fetal hemoglobin and may also exert beneficial effects on red blood cell hydration, vascular wall adherence, and suppression of the granulocyte and reticulocyte counts; dosage is titrated to maintain a white cell count between 5000 and 8000/μL. White cells and reticulocytes may play a major role in the pathogenesis of sickle cell crisis, and their suppression may be an important side benefit of hydroxyurea therapy. Hydroxyurea should be considered in patients experiencing repeated episodes of acute chest syndrome or with more than three crises per year requiring hospitalization. Hydroxyurea offers broad benefits to most patients whose disease is severe enough to impair their functional status, and it may improve survival. Fetal hemoglobin levels increase in most patients within a few months.

II-62. and II-63. **The answers are E and E, respectively.** *(Chap. 95)* The peripheral blood smear shows macrocytosis, anisocytosis, and poikilocytosis with a hypersegmented (greater

TABLE II-63 Causes of Megaloblastic Anemia

Cobalamin deficiency or abnormalities of cobalamin metabolism (see Tables 95-3 and 95-4 in HPIM 20)
Folate deficiency or abnormalities of folate metabolism (see Table 95-5 in HPIM 20)
Therapy with antifolate drugs (e.g., methotrexate)
Independent of either cobalamin or folate deficiency and refractory to cobalamin and folate therapy:
Some cases of acute myeloid leukemia, myelodysplasia
Therapy with drugs interfering with synthesis of DNA (e.g., cytosine arabinoside, hydroxyurea, 6-mercaptopurine, azidothymidine)
Orotic aciduria (responds to uridine)
Thiamine-responsive

than five lobes) polymorphonuclear cell. These findings are diagnostic of megaloblastic anemia (Table II-63). In cases of severe anemia, there may also be reduction in white blood cell and platelet count. The most common causes of megaloblastic anemia are folate and cobalamin deficiency. This patient most likely has pernicious anemia given her normal diet and absence of other symptoms. The next best test will be a serum vitamin B_{12} level. In patients with cobalamin deficiency sufficient to cause anemia or neuropathy, the serum methylmalonic acid (MMA) level is raised. Sensitive methods for measuring MMA and homocysteine in serum have been introduced and recommended for the early diagnosis of cobalamin deficiency, even in the absence of hematologic abnormalities or subnormal levels of serum cobalamin. Serum MMA levels fluctuate, however, in patients with renal failure. Serum homocysteine is raised in both early cobalamin and folate deficiency but may be raised in other conditions (e.g., chronic renal disease, alcoholism, smoking, pyridoxine deficiency, hypothyroidism, and therapy with steroids, cyclosporine, and other drugs).

II-64. **The answer is B.** *(Chap. 96)* This patient presents with the classic signs, symptoms, and laboratory abnormalities of paroxysmal nocturnal hemoglobinuria (PHN). PNH is an acquired chronic hemolytic anemia (HA) characterized by persistent intravascular hemolysis with occasional or frequent recurrent exacerbations. In addition to (1) hemolysis, there may be (2) pancytopenia and (3) a distinct tendency to venous thrombosis. This triad makes PNH a truly unique clinical condition; however, when not all of these three features are manifest on presentation, the diagnosis is often delayed, although it can always be made by appropriate laboratory investigations. When seeking medical attention, the patient may report that one morning, she or he "passed blood instead of urine" (Figure II-64). This distressing or frightening event may be regarded as the classic

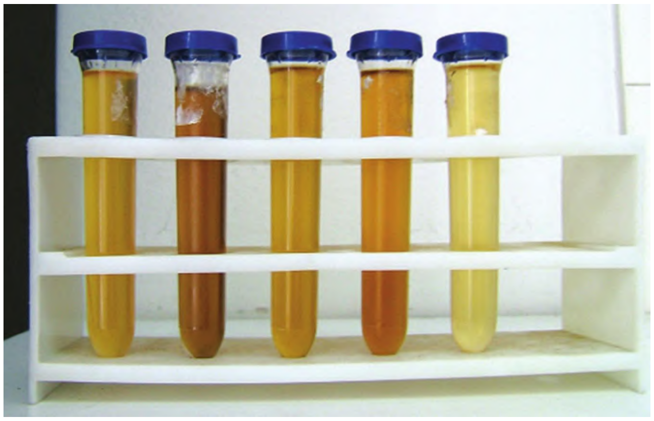


FIGURE II-64 Consecutive urine samples from a patient with paroxysmal nocturnal hemoglobinuria (PNH). The variation in the severity of hemoglobinuria within hours is probably unique to this condition.

presentation; however, more frequently, this symptom is not noticed or not reported. Indeed, the patient often presents simply as a problem in the differential diagnosis of *anemia*, whether symptomatic or discovered incidentally. Sometimes the anemia is associated from the outset with neutropenia, thrombocytopenia, or both, thus signaling an element of bone marrow failure. Some patients may present with recurrent attacks of severe abdominal pain eventually found to be related to thrombosis in abdominal veins, or attributable to nitric oxide depletion associated with intravascular hemolysis. When thrombosis affects the hepatic vein it may produce acute hepatomegaly and ascites, i.e., a full-fledged Budd-Chiari syndrome, which, in the absence of liver disease, ought to raise the suspicion of PNH. The most consistent blood finding is anemia, which may range from mild to moderate to very severe. The anemia is usually normocytic to macrocytic, with unremarkable red cell morphology. The definitive diagnosis of PNH must be based on the demonstration that a substantial proportion of the patient's red cells have an increased susceptibility to complement (C), due to the deficiency on their surface of proteins (particularly CD59 and CD55) that normally protect the red cells from activated C. The sucrose hemolysis test is unreliable; in contrast, the acidified serum (Ham) test is highly reliable but is carried out only in a few labs. The gold standard today is flow cytometry, which can be carried out on granulocytes as well as on red cells, and has a very high sensitivity. In PNH, characteristically, one sees a bimodal distribution of cells, with a discrete population that is CD59 and CD55 negative. Although very small populations of CD59(-) cells are of interest in terms of pathophysiology (particularly of aplastic anemia), no patient should be diagnosed with PNH unless their proportion is substantial: in first approximation at least 5% of the total red cells and at least 20% of the total granulocytes. Hereditary spherocytosis will present with numerous spherocytes in the peripheral blood, and the presence of osmotic fragility is the main diagnostic test for hereditary spherocytosis. The presence of the Donath-Landsteiner antibody will prove paroxysmal cold hemoglobinuria (occurring mostly in children, usually triggered by a viral infection, usually self-limited). Mutations in the 6-phosphate dehydrogenase (G6PD) gene lead to G6PD deficiency, which can lead to hemolysis with treatment of certain drugs. Blood cultures would identify septicemia which can contribute to intravascular hemolysis.

II-65. **The answer is A.** *(Chap. 96)* The peripheral blood smear in Figure II-65 shows bite cells (arrow), anisocytosis, and spherocytes. The combination of the peripheral smear, jaundice, and hyperbilirubinemia 1 day after receiving sulfamethoxazole makes glucose 6-phosphate dehydrogenase (G6PD) deficiency most likely. G6PD deficiency is widely distributed in tropical and subtropical parts of the world (Africa, southern Europe, the Middle East, Southeast Asia, and Oceania) and wherever people from those areas have migrated. A conservative estimate is that at least 400 million people have a *G6PD* deficiency gene. In several of these areas, the frequency of a *G6PD* deficiency gene may be as high as 20% or more. The *G6PD* gene is X-linked; thus, males have only one *G6PD* gene (i.e., they are hemizygous for this gene). Therefore, they must be either normal or G6PD deficient. Hemolytic anemia in patients with G6PD deficiency can develop as a result of fava beans, infections, and drugs. Common drugs include primaquine, dapsone, sulfamethoxazole, and nitrofurantoin. Typically, a hemolytic attack starts with malaise, weakness, and abdominal or lumbar pain. After an interval of several hours to 2–3 days, the patient develops jaundice and often dark urine. The onset can be extremely abrupt, especially with favism in children. There may be hemoglobinemia, hemoglobinuria, high lactate dehydrogenase, and low or absent plasma haptoglobin. G6PD deficiency may be diagnosed by semiquantitative or quantitative red blood cell tests or by DNA testing. Hemolytic-uremic syndrome and thrombotic thrombocytopenic purpura cause microangiopathic hemolytic anemia with prominent schistocytes. Iron deficiency causes a microcytic and hypochromic anemia.

II-66. **The answer is B.** *(Chap. 96)* This patient has autoimmune hemolytic anemia (AIHA) with development of warm IgG antibodies due to ceftriaxone exposure (Table II-66). AIHA is a serious condition; without appropriate treatment, it may have a mortality of approximately 10%. The onset is often abrupt and can be dramatic. The hemoglobin level can drop within days to as low as 4 g/dL, the massive red cell removal will produce jaundice, and sometimes the spleen is enlarged. When this triad is present, the suspicion of AIHA must be high.

TABLE II-66 Classification of Acquired Immune Hemolytic Anemias

	Type of Antibody	
Clinical Setting	Cold, Mostly IgM, Optimal Temperature 4–30°C	Warm, Mostly IgG, Optimal Temperature 37°C; or Mixed
Primary	CAD	AIHA (idiopathic)
Secondary to viral infection	EBV CMV Other	HIV Viral vaccines
Secondary to other infection	Mycoplasma infection: paroxysmal cold hemoglobinuria	
Secondary to/associated with other disease	CAD in: Waldenström disease Lymphoma	AIHA in: SLE CLL Other malignancy Chronic inflammatory disorders (e.g., IBD) After allogeneic HSCT After immune check-point modulating drugs
Secondary to drugs: drug-induced immune hemolytic anemia	Small minority (e.g., with lenalidomide)	Majority: currently most common culprit drugs are cefotetan, ceftriaxone, piperacillin
	Drug-dependent: antibody destroys red cells only when drug is present (e.g., rarely penicillin)	
	Drug-independent: antibody can destroy red cells even when drug is no longer present (e.g., methyldopa)	

Abbreviations: AIHA, autoimmune hemolytic anemia; CAD, cold agglutinin disease; CLL, chronic lymphocytic leukemia; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; Ig, immunoglobulin; HSCT, hematopoietic stem cell transplantation; IBD, inflammatory bowel disease; SLE, systemic lupus erythematosus.

The diagnostic test for AIHA is the direct antiglobulin (Coombs) test, which detects the presence of antibody on the red cells. When the test is positive, it clinches the diagnosis; when it is negative, the diagnosis is unlikely. The immediate treatment almost invariably includes transfusion of red cells. This may pose a special problem because, if the antibody involved is nonspecific, all of the blood units cross-matched will be incompatible. Whenever the anemia is not immediately life-threatening, blood transfusion should be withheld (because compatibility problems may increase with each unit of blood transfused), and medical treatment started immediately with prednisone (1 mg/kg per day), which will produce a remission promptly in at least one-half of patients. Rituximab (anti-CD20) was regarded as second-line treatment, but it is increasingly likely that a relatively low dose (100 mg/wk × 4) of rituximab together with prednisone is becoming a first-line standard. It is especially encouraging that this approach seems to reduce the rate of relapse, a common occurrence in AIHA. 6-Phosphate dehydrogenase (G6PD) deficiency is unlikely in this previously healthy female only exposed to ceftriaxone. ADAMTS-13 activity assay is used to diagnose thrombotic thrombocytopenic purpura. Flow cytometry may be used to diagnose paroxysmal nocturnal hemoglobinuria. Hemoglobin electrophoresis is used to diagnose congenital hemoglobinopathies.

II-67. **The answer is E.** *(Chap. 98)* This patient has a pancytopenia with reductions of white blood cells, red blood cells, and platelets. All of the listed diagnoses are on the differential diagnosis for pancytopenia except for parvovirus infection (Table II-67). Isolated temporary red cell failure occurs in transient aplastic crisis of hemolytic anemias due to acute parvovirus infection. Parvovirus does not cause pancytopenia.

II-68. **The answer is D.** *(Chap. 98)* This patient likely has idiopathic myelodysplastic syndrome (MDS). The MDSs are a heterogeneous group of hematologic disorders broadly characterized by both (1) cytopenias due to bone marrow failure and (2) a high risk of development of acute myeloid leukemia (Table II-68). Anemia, often with

TABLE II-67 Differential Diagnosis of Pancytopenia

Pancytopenia with Hypocellular Bone Marrow	
Acquired aplastic anemia	
Constitutional aplastic anemia (Fanconi anemia, dyskeratosis congenita, and others)	
Hypocellular myelodysplastic syndrome	
Rare aleukemic leukemia	
Some acute lymphoid leukemia	
Rare lymphomas of bone marrow	
Copper deficiency	
Pancytopenia with Cellular Bone Marrow	
Primary bone marrow diseases	Secondary to systemic diseases
Myelodysplastic syndromes	Systemic lupus erythematosus
Paroxysmal nocturnal hemoglobinuria	Hypersplenism
Myelofibrosis	B_{12}, folate deficiency
Aleukemic leukemia	Copper deficiency
Myelophthisis	Alcohol
Bone marrow lymphoma	HIV infection
Hairy cell leukemia	Brucellosis
	Sarcoidosis
	Tuberculosis
	Leishmaniasis
	Sepsis
Hypocellular Bone Marrow ± Pancytopenia	
Q fever	
Legionnaires disease	
Anorexia nervosa, starvation	
Mycobacterium	

TABLE II-68 World Health Organization Classification of Myelodysplastic Syndromes/Neoplasms

Name	Ring Sideroblasts	Myeloblasts	Karyotype
MDS with single lineage dysplasia (MDS-SLD)	<15% (<5%)[a]	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with multilineage dysplasia (MDS-MLD)	<15% (<5%)[a]	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with ring sideroblasts (MDS-RS)			
MDS-RS with single lineage dysplasia (MDS-RS-SLD)	≥15%/≥5%[a]	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS-RS with multilineage dysplasia (MDS-RS-MLD)	≥15% / ≥5%[a]	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with isolated del(5q)	None or any	BM <5%, PB <1%, no Auer rods	del(5q) alone or with 1 additional abnormality except −7 or del (7q)
MDS with excess blasts (MDS-EB)			
MDS-EB-1	None or any	BM 5–9% or PB 2–4%, no Auer rods	Any
MDS-EB-2	None or any	BM 10–19% or PB 5–19% or Auer rods	Any
MDS, unclassifiable (MDS-U)			
• With 1% blood blasts	None or any	BM <5%, PB = 1%, no Auer rods	Any
• With single lineage dysplasia and pancytopenia	None or any	BM <5%, PB = 1%, no Auer rods	Any
• Based on defining cytogenetic abnormality	15%	BM <5%, PB = 1%, no Auer rods	MDS-defining abnormality
Refractory cytopenia of childhood	None	BM <5%, PB <2%	Any

[a] If *SF3B1* mutation is present.

Abbreviations: BM, bone marrow; MDS, myelodysplastic syndrome; PB, peripheral blood.

thrombocytopenia and neutropenia, occurs with dysmorphic (abnormal-appearing) and usually cellular bone marrow, which is evidence of ineffective blood cell production. In patients with "low-risk" MDS, marrow failure dominates the clinical course. In other patients, myeloblasts are present at diagnosis, chromosomes are abnormal, and the "high risk" is due to leukemic progression. MDS may be fatal due to the complications of pancytopenia or the incurability of leukemia, but a large proportion of patients will die of concurrent disease, the comorbidities typical in an elderly population. Idiopathic MDS is a disease of the elderly; the mean age at onset is older than 70 years. There is a slight male predominance. MDS is a relatively common form of bone marrow failure, with reported incidence rates of 35 to >100 per million persons in the general population and 120 to >500 per million persons in older adults. MDS is rare in children but is increased in children with Down syndrome. MDS is associated with environmental exposures such as radiation and benzene. Secondary MDS occurs as a late toxicity of cancer treatment, usually a combination of radiation and the radiomimetic alkylating agents such as busulfan, nitrosourea, or procarbazine (with a latent period of 5–7 years) or the DNA topoisomerase inhibitors (2-year latency). Anemia dominates the early course of MDS. Most symptomatic patients complain of the gradual onset of fatigue and weakness, dyspnea, and pallor, but at least one-half of patients are asymptomatic, and their MDS is discovered only incidentally on routine blood counts. The physical examination is typical for signs of anemia, with approximately 20% of patients having splenomegaly. Some unusual skin lesions, including Sweet syndrome (febrile neutrophilic dermatosis), occur with MDS. Median survival times of patients with MDS vary widely, but prognosis worsens with increasing percent blasts in bone marrow, cytogenetic abnormalities, and lineages affected by cytopenia. Only hematopoietic stem cell transplantation offers cure of MDS. The current survival rate in selected patient cohorts is approximately 50% at 3 years and is improving. New epigenetic modulator drugs are believed to act through a demethylating mechanism to alter gene regulation and allow differentiation to mature blood cells from the abnormal MDS stem cell. Azacitidine and decitabine are two epigenetic modifiers frequently used in bone marrow failure clinics. Azacitidine improves blood counts and survival in MDS compared with best supportive care.

II-69. **The answer is E.** *(Chap. 99)* Thrombocytosis or thrombocythemia is typically defined as a platelet count of >450,000–500,000. Typically additional evaluation is not warranted until the platelet count rises above 700,000. Iron-deficiency anemia may cause an elevated platelet count. Essential thrombocytosis (ET; other designations include *essential thrombocythemia*, *idiopathic thrombocytosis*, *primary thrombocytosis*, and *hemorrhagic thrombocythemia*) is a clonal hematopoietic stem cell disorder associated with mutations in *JAK2* (V617F), *MPL*, and *CALR* and manifested clinically by overproduction of platelets without a definable cause. ET has an incidence of 1–2/100,000 and a distinct female predominance in association with *JAK2* V617F, *CALR*, and *MPL* mutations. Canonical myeloproliferative neoplasm driver mutations distinguish 90% of ET patients from the more common nonclonal, reactive forms of thrombocytosis. Mutation-negative ET patients may have a hereditary form of thrombocytosis. Perhaps no other condition in clinical medicine has caused otherwise astute physicians to intervene inappropriately more often than thrombocytosis, particularly if the platelet count is $>1 \times 10^6/\mu L$. It is commonly believed that a high platelet count causes thrombosis; however, no controlled clinical study has ever established this association, and in patients younger than age 60 years, the incidence of thrombosis was not greater in patients with thrombocytosis than in age-matched controls, and tobacco use appears to be the most important risk factor for thrombosis in ET patients. Survival of ET patients is not different from the general population regardless of the driver mutation. An elevated platelet count in an asymptomatic patient without cardiovascular risk factors or tobacco use requires no therapy. Indeed, before any therapy is initiated in a patient with thrombocytosis, the cause of symptoms must be clearly identified as due to the elevated platelet count. When the platelet count rises above $1 \times 10^6/\mu L$, a substantial quantity of high-molecular-weight von Willebrand multimers are removed from the circulation and destroyed by the enlarged platelet mass, resulting in an acquired form of von Willebrand's disease. This can be identified by a reduction in ristocetin cofactor activity. In this situation, aspirin could promote hemorrhage.

II-70. and II-71. The answers are C and D, respectively. *(Chaps. 99)* This patient has polycythemia, likely due to polycythemia vera (PV), with the elevation of hemoglobin, white blood cell count, and platelets. The next step in his evaluation is measurement of red blood cell (RBC) mass. After finding an elevated RBC mass, measurement of erythropoietin levels will distinguish between PV and other causes of polycythemia such as renal cell carcinoma, lung disease, hypoxemic states, or chronic carbon monoxide poisoning (Table II-71). PV is a clonal disorder involving a multipotent hematopoietic progenitor cell in which phenotypically normal red cells, granulocytes, and platelets accumulate in the absence of a recognizable physiologic stimulus. The etiology of PV is unknown. A mutation in the autoinhibitory pseudokinase domain of the tyrosine kinase JAK2, which replaces valine with phenylalanine (V617F) causing constitutive kinase activation, appears to have a central role in the pathogenesis of PV. A markedly elevated RBC mass and a low erythropoietin level can confirm the diagnosis of PV. PV is generally an indolent disorder, the clinical course of which is measured in decades, and its management should reflect its tempo. Thrombosis due to erythrocytosis is the most significant complication and often the presenting manifestation, and maintenance of the hemoglobin level at ≤140 g/L (14 g/dL; hematocrit <45%) in men and ≤120 g/L (12 g/dL; hematocrit <42%) in women is mandatory to avoid thrombotic complications. Phlebotomy serves initially to reduce hyperviscosity by bringing the red blood cell mass into the normal range while further expanding the plasma volume. Periodic phlebotomies thereafter serve to maintain the red cell mass within the normal range and to induce a state of iron deficiency that prevents an accelerated re-expansion of the red cell mass. Neither phlebotomy nor iron deficiency increases the platelet count relative to the effect of the disease itself, and thrombocytosis is not correlated with thrombosis in PV, in contrast to the strong correlation between erythrocytosis and thrombosis in this disease. The use of salicylates as a tonic against thrombosis in PV patients is not only

TABLE II-71 Causes of Erythrocytosis

Relative Erythrocytosis	
Hemoconcentration secondary to dehydration, diuretics, ethanol abuse, androgens, or tobacco abuse	
Absolute Erythrocytosis	
Hypoxia	Tumors
Carbon monoxide intoxication	Hypernephroma
High-oxygen-affinity hemoglobins	Hepatoma
High altitude	Cerebellar hemangioblastoma
Pulmonary disease	Uterine myoma
Right-to-left cardiac or vascular shunts	Adrenal tumors
Sleep apnea syndrome	Meningioma
Hepatopulmonary syndrome	Pheochromocytoma
Renal disease	Drugs
Renal artery stenosis	Androgens
Focal sclerosing or membranous glomerulonephritis	Recombinant erythropoietin
	Familial (with normal hemoglobin function)
Postrenal transplantation	Erythropoietin receptor mutations
Renal cysts	*VHL* mutations (Chuvash polycythemia)
Bartter syndrome	2,3-BPG mutation
	PHD2 and HIF2α mutations
	Polycythemia vera

Abbreviations: 2,3-BPG, 2,3-bisphosphoglycerate; HIF, hypoxia induced factor; PHD2, prolyl hydroxylase 2; VHL, von Hippel-Lindau.

potentially harmful if the red cell mass is not controlled by phlebotomy, but it is also an unproven remedy. Anticoagulants are only indicated when a thrombosis has occurred and can be difficult to monitor if the red cell mass is substantially elevated because of the artifactual imbalance between the test tube anticoagulant and plasma that occurs when blood from these patients is assayed for prothrombin or partial thromboplastin activity. Imatinib is a Bcr-Abl tyrosine kinase inhibitor typically used in cases of chronic myelogenous leukemia and is not efficacious in PV.

II-72. **The answer is E.** *(Chap. 100)* This patient has acute myeloid leukemia (AML). The peripheral smear shows a uniform population of primitive myeloblasts with immature chromatin, nucleoli in some cells, and primary cytoplasmic granules. Several factors predict the outcome of AML patients treated with chemotherapy; they should be used for risk stratification and treatment guidance. Chromosome findings at diagnosis currently provide the most important independent prognostic information. Several reports have categorized patients as having favorable, intermediate, or adverse cytogenetic risk based on the presence of structural and/or numerical aberrations. Patients with t(15;17) have a very good prognosis (~85% cured), and those with t(8;21) and inv(16) have a good prognosis (~55% cured), whereas those with no cytogenetic abnormality have an intermediate outcome risk (~40% cured). Patients with a complex karyotype, t(6;9), inv(3), or −7 have a very poor prognosis. Another cytogenetic subgroup, the monosomal karyotype, has been suggested to adversely impact the outcome of AML patients other than those with t(15;17), t(8;21), or inv(16) or t(16;16). The monosomal karyotype subgroup is defined by the presence of at least two autosomal monosomies (loss of chromosomes other than Y or X) or a single autosomal monosomy with additional structural abnormalities.

II-73. **The answer is E.** *(Chap. 100)* Acute promyelocytic leukemia (APL) is a highly curable subtype of acute myelogenous leukemia (AML), and approximately 85% of these patients achieve long-term survival with current approaches. APL has long been shown to be responsive to cytarabine and daunorubicin, but previously, patients treated with these drugs alone frequently died from disseminated intravascular coagulation (DIC) induced by the release of granule components by the chemotherapy-treated leukemia cells. However, the prognosis of APL patients has changed dramatically from adverse to favorable with the introduction of tretinoin, an oral drug that induces the differentiation of leukemic cells bearing the characteristic translocation [t(15;17)], where disruption of the *RARA* gene encoding a retinoid acid receptor occurs. Tretinoin decreases the frequency of DIC but produces another complication called the APL differentiation syndrome. Occurring within the first 3 weeks of treatment, it is characterized by fever, fluid retention, dyspnea, chest pain, pulmonary infiltrates, pleural and pericardial effusions, and hypoxemia. The syndrome is related to adhesion of differentiated neoplastic cells to the pulmonary vascular endothelium. Glucocorticoids, chemotherapy, and/or supportive measures can be effective for management of the APL differentiation syndrome. Temporary discontinuation of tretinoin is necessary in cases of severe APL differentiation syndrome (i.e., patients developing renal failure or requiring admission to the intensive care unit due to respiratory distress). The mortality rate of this syndrome is about 10%. Acyclovir is used to treat herpes virus infection. Daunorubicin is an anthracycline chemotherapy agent commonly used in the therapy of AML and acute lymphoblastic leukemia (ALL); it is not specific to APL. Rituximab is a monoclonal antibody against CD20 used in a wide assortment of autoimmune and malignant diseases. Sildenafil is a PDE5 inhibitor used for treatment of erectile dysfunction and pulmonary arterial hypertension.

II-74. **The answer is B.** *(Chap. 101)* Chronic myeloid leukemia (CML) is a clonal hematopoietic stem cell disorder. The disease is driven by the *BCR-ABL1* chimeric gene product, that codes for a constitutively active tyrosine kinase, resulting from a reciprocal balanced translocation between the long arms of chromosomes 9 and 22, t(9;22)(q34.1;q11.2), known as the Philadelphia chromosome (Ph). Before the era of selective BCR-ABL1 tyrosine kinase inhibitors (TKIs), the median survival in CML was 3–7 years, and the 10-year survival rate was 30% or less. Introduced into standard CML therapy in 2000, TKIs have revolutionized the treatment, natural history, and prognosis of CML. Today, the estimated 10-year survival rate with imatinib mesylate, the first BCR-ABL1 TKI approved, is 85%. Allogeneic stem cell transplantation (SCT), a curative approach but one that involves more risks, is now more often offered as second- or third-line therapy after failure of TKIs. There are no familial associations in CML. CML is not a frequent secondary leukemia following therapy of other cancers with alkylating agents and/or radiation. Exposure to ionizing radiation (e.g., nuclear accidents, radiation treatment for ankylosing spondylitis or cervical cancer) has increased the risk of CML, which peaks at 5–10 years after exposure and is dose related. Most patients with CML (90%) present in the indolent or chronic phase. Depending on the timing of diagnosis, patients are often asymptomatic (if the diagnosis is discovered during health care screening tests). Common symptoms, when present, are manifestations of anemia and splenomegaly. These may include fatigue, malaise, weight loss (if high leukemia burden), or early satiety and left upper quadrant pain or masses (from splenomegaly).

II-75. **The answer is C.** *(Chap. 102)* In acute lymphoblastic leukemia (ALL), the malignant clone arises from hematopoietic progenitors in the bone marrow or lymphatic system resulting in an increase of immature nonfunctioning leukemic cells. Infiltration of bone marrow leads to anemia, granulocytopenia, and thrombocytopenia with the clinical manifestations of fatigue, weakness, infection, and hemorrhages. Patients with some rare congenital chromosomal abnormalities have a higher risk of development of acute leukemia; e.g., Klinefelter syndrome, Fanconi anemia, Bloom syndrome, ataxia telangiectasia, and neurofibromatosis. There is a 20-fold increased incidence of leukemia in patients with Down syndrome, in whom ALL is increased in childhood and acute myelogenous leukemia (AML) at an older age. Genetic predisposition may play a part in acute leukemia even, when not associated with another inherited disease, as the identical twin of a leukemic child has a fivefold risk of developing acute leukemia. Human T-cell leukemia virus I (HTLV-I), endemic in Japan and the Caribbean, is the etiological agent for adult T-cell leukemia/lymphoma, an aggressive adult T-cell leukemia (see Chap. 196 in HPIM 20). In the endemic African type of Burkitt lymphoma, the Epstein-Barr virus, a DNA virus of the herpes family, has been implicated as a potential causative agent. The examination of the cerebrospinal fluid is an essential routine diagnostic measure for ALL due to the high risk of central nervous system (CNS) involvement to help guide therapy. More than 70% of adult ALLs are of B-cell origin, and the most frequent immunological subtype, common ALL, is characterized by the presence of ALL antigen, a glycoprotein (gp100/CD10). Approximately 25% of adult ALLs belong to the T-cell lineage. *BCR-ABL1*-like ALL is characterized by genetic lesions similar to Ph+ ALL, associated with *IKZF1* deletion, *CLRF2* overexpression, and tyrosine kinase activating rearrangements involving *ABL1*, *JAK2*, *PDGFRB*, and several others. The frequency is 10% in children and 25–30% in young adults, but does not increase further with age. Treatment may be directed at the underlying genetic pattern with BCR-ABL inhibitors (e.g., dasatinib) or JAK2 inhibitors (e.g., ruxolitinib).

II-76. **The answer is C.** *(Chap. 103)* This peripheral blood smear shows a preponderance of mature lymphocytes typical of the diagnosis of chronic lymphocytic leukemia (CLL). The presentation of CLL most commonly occurs as an incidental diagnosis made at the time of medical evaluation for another cause. In this regard, CLL is most commonly diagnosed on routine blood work demonstrating an elevated lymphocyte count in asymptomatic individuals, although some patients present with symptoms and require early therapy. In the presence of either an elevated total white blood cell (WBC) count with lymphocytic predominance or a normal WBC with a differential showing a marked lymphocytosis, the next step is to perform flow cytometry on the peripheral blood (Table II-76). In CLL, this will reveal the typical immunophenotype that includes the typical B-cell markers CD19, CD20, CD22, CD23, the T-cell marker CD5 (CD5 is also expressed on the B1 subset of B cells that typically has unmutated immunoglobulin and responds to antigens independent of cognate T-cell help), and dim surface immunoglobulin of either kappa or lambda type. Atypical phenotypes can be seen as well and usually can be differentiated on the basis

TABLE II-76 Typical Immunophenotype of Chronic Lymphocytic Leukemia Compared With Other B-Cell Malignancies

Disease	CD5	CD10	CD19	CD20	CD23	Cyclin D1	Surface Ig
CLL	+	−	+	+ (dim)	+	−	+ (dim)
Mantle cell lymphoma	+	−	+	+ (mod/bright)	−	+	+ (mod/bright)
Marginal zone lymphoma	−/+	−	+	+ (mod/bright)	−/+	−	+ (mod/bright)
Follicular lymphoma	−	+	+	+	+	−	

Abbreviation: CLL, chronic lymphocytic leukemia; Ig, immunoglobulin.

of morphology, cytogenetics, or clinical presentation. In cases in which the clonal B cell count based on flow cytometry is ≥5 × 10^9/L, no further workup is needed to confirm the diagnosis of CLL.

Induction chemotherapy would be indicated for acute leukemia which this patient does not have. Positron emission tomography (PET)-CT and CT scans are not helpful in the diagnosis of leukemia. Imaging with CT scan is usually not necessary unless there are symptoms and concern for intra-abdominal nodes out of proportion to peripheral nodes. Bone marrow biopsy is not undertaken until therapy is initiated except in cases of unexplained cytopenias.

II-77. The answer is D. *(Chaps. 104 and 105)* Shown in the image is a classic Reed-Sternberg (RS) cell. This is diagnostic of Hodgkin lymphoma (HL). HL is a malignancy of mature B lymphocytes. The overwhelming majority of patients with HL will be cured with either chemotherapy alone, or a combination of chemotherapy and radiation therapy, which is true of other lymphomas, such as Burkitt lymphoma and diffuse large B-cell lymphoma. Epstein-Barr virus is associated with the development of HL. Interestingly, 97% of Hodgkin RS cells in classic HL harbor genetic aberrations in the PD-L1 locus on chromosome 9p24.1, resulting in overexpression of PD-L1 protein, the ligand for the inhibitory PD-1 receptor on immune cells. This is one mechanism in which the Hodgkin RS cell may be able to avoid immune destruction in its inflammatory microenvironment and may contribute to the generalized immune suppression in HL patients. The existence of the t(14;18) mutation and abnormal expression of BCL-2 protein are confirmatory for follicular lymphoma, not Hodgkin lymphoma.

II-78. The answer is E. *(Chap. 106)* A “dry tap” is defined as the inability to aspirate bone marrow and is reported in approximately 4% of attempts (Table II-78). It is rare in the case of normal bone marrow. The differential diagnosis includes metastatic carcinoma infiltration (17%), chronic myeloid leukemia (15%), myelofibrosis (14%), hairy cell leukemia (10%), acute leukemia (10%), and lymphomas including Hodgkin disease (9%).

TABLE II-78 Differential Diagnosis of “Dry Tap”—Inability to Aspirate Bone Marrow

Dry taps occur in about 4% of attempts and are associated with:	
Metastatic carcinoma infiltration	17%
Chronic myeloid leukemia	15%
Myelofibrosis	14%
Hairy cell leukemia	10%
Acute leukemia	10%
Lymphomas, Hodgkin disease	9%
Normal marrow	Rare

II-79. **The answer is B.** *(Chap. 106)* The diagnostic criteria for chronic eosinophilic leukemia and the hypereosinophilic syndrome first require the presence of persistent blood eosinophilia ≥1500/μl, increased marrow eosinophils, and <20% myeloblasts in blood or marrow. Additional disorders that must be excluded include all causes of reactive eosinophilia, primary neoplasms associated with eosinophilia (e.g., T-cell lymphoma, Hodgkin disease, acute lymphocytic leukemia, mastocytosis, chronic myeloid leukemia, acute myeloid leukemia, myelodysplasia, myeloproliferative syndromes), and T-cell reaction with increased IL-5 or cytokine production. If these entities have been excluded and the myeloid cells show a clonal chromosome abnormality and blast cells (>2%) are present in peripheral blood or are increased in marrow (but <20%), then the diagnosis is chronic eosinophilic leukemia. Patients with hypereosinophilic syndrome and chronic eosinophilic leukemia may be asymptomatic (discovered on routine testing) or present with systemic findings such as fever, shortness of breath, new neurologic findings, or rheumatologic findings. The heart, lungs, and central nervous system are most often affected by eosinophil-mediated tissue damage.

II-80. **The answer is C.** *(Chap. 107)* The most important differential diagnosis in patients with myeloma involves their separation from individuals with monoclonal gammopathy of undetermined significance (MGUS) or smoldering multiple myeloma (SMM) (Table II-80). MGUS is vastly more common than myeloma, occurring in 1% of the population aged >50 years and in up to 10% of individuals aged >75 years. The diagnostic criteria for MGUS, SMM, and myeloma are described below. This patient has smoldering myeloma based on 20% bone marrow plasma cells without any myeloma-defining events (normal creatinine and calcium). The use of fluorine-18 fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET)/CT is recommended to distinguish between smoldering and active MM. No specific intervention is indicated for patients with MGUS. Follow-up once a year or less frequently is adequate except in higher risk MGUS, where serum protein electrophoresis, complete blood count,

TABLE II-80 **Diagnostic Criteria for Multiple Myeloma, Myeloma Variants, and Monoclonal Gammopathy of Undetermined Significance**

Monoclonal Gammopathy of Undetermined Significance (MGUS)
Serum monoclonal protein (non-IgM type) <30 g/L Clonal bone marrow plasma cells <10%* Absence of myeloma-defining events or amyloidosis that can be attributed to the plasma cell proliferative disorder
Smoldering Multiple Myeloma (Asymptomatic Myeloma)
Both criteria must be met: • Serum monoclonal protein (IgG or IgA) ≥30 g/L or urinary monoclonal protein ≥500 mg per 24 h and/or clonal bone marrow plasma cells 10–60% • Absence of myeloma-defining events or amyloidosis
Symptomatic Multiple Myeloma
Clonal bone marrow plasma cells or biopsy-proven bony or extramedullary plasmacytoma[a] and any one or more of the following myeloma defining events: • Evidence of one or more end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically: • Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL) • Renal insufficiency: creatinine clearance <40 mL/min[b] or serum creatinine >177 μmol/L (>2 mg/dL) • Anemia: hemoglobin value of >20 g/L below the lower limit of normal, or a hemoglobin value <100 g/L • Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT[c] • Any one or more of the following biomarkers of malignancy: • Clonal bone marrow plasma cell percentage[a] ≥60% • Involved: uninvolved serum free light chain ratio[d] ≥100 • >1 focal lesions on MRI studies[e]

(*continued*)

TABLE II-80 Diagnostic Criteria for Multiple Myeloma, Myeloma Variants, and Monoclonal Gammopathy of Undetermined Significance (*Continued*)

Nonsecretory Myeloma
No M protein in serum and/or urine with immunofixation[f] Bone marrow clonal plasmacytosis ≥10% or plasmacytoma[a] Myeloma-related organ or tissue impairment (end-organ damage, as described above)
Solitary Plasmacytoma
Biopsy-proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells Normal bone marrow with no evidence of clonal plasma cells[a] Normal skeletal survey and MRI (or CT) of spine and pelvis (except for the primary solitary lesion) Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, or bone lesions (CRAB) that can be attributed to a lymphoplasma cell proliferative disorder
POEMS Syndrome
All of the following four criteria must be met: 1. Polyneuropathy 2. Monoclonal plasma cell proliferative disorder 3. Any one of the following: (a) sclerotic bone lesions; (b) Castleman disease; (c) elevated levels of vascular endothelial growth factor (VEGF) 4. Any one of the following: (a) organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy), (b) extravascular volume overload (edema, pleural effusion, or ascites), (c) endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, and pancreatic), (d) skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomata, plethora, acrocyanosis, flushing, and white nails), (e) papilledema, (f) thrombocytosis/polycythemia[g]

[a] Clonality should be established by showing κ/λ-light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used.

[b] Measured or estimated by validated equations.

[c] If bone marrow has less than 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement.

[d] These values are based on the serum Freelite assay (The Binding Site Group, Birmingham, UK). The involved free light chain must be ≥100 mg/L.

[e] Each focal lesion must be 5 mm or more in size.

[f] A small M component may sometimes be present.

[g] These features should have no attributable other causes and have temporal relation with each other.

Abbreviation: PET-CT, ^{18}F-fluorodeoxyglucose PET with CT; POEMS, polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes.

creatinine, and calcium should be repeated every 6 months. About 10% of patients have SMM and will have an indolent course demonstrating only slow progression of disease over many years. For patients with SMM, no specific therapeutic intervention is indicated, although early intervention with lenalidomide and dexamethasone may prevent progression from high-risk SMM to active MM. At present, patients with SMM only require antitumor therapy when myeloma-defining events are identified. Patients with symptomatic and/or progressive myeloma require therapeutic intervention, which may include dexamethasone and lenalidomide.

II-81. **The answer is A.** *(Chap. 107)* The patient presents with pneumococcal pneumonia and evidence of hypercalcemia, renal failure, and a wide protein (gamma) gap suggestive of an M protein. These findings are classic for multiple myeloma. Although patients appear to be making large quantities of immunoglobulins, they are in fact generally monoclonal, and patients actually have functional hypogammaglobulinemia related to both decreased production and increased destruction of normal antibodies. This hypogammaglobulinemia predisposes patients to infections, most commonly pneumonia with *Pneumococcus* or *Staphylococcus aureus* or gram-negative pyelonephritis. Bone marrow biopsy would confirm the presence of clonal plasma cells and define the quantity, which will help define treatment options. A serum protein electrophoresis would also be indicated to prove the presence of the M protein suspected by the wide protein gap. Although HIV may be associated with kidney injury, both acute and chronic, hypercalcemia would be an unusual feature. There is no clinical history of aspiration, and the location of infiltrate (upper lobe) is unusual for aspiration. Sweat chloride testing is not indicated because there is no suspicion for cystic fibrosis. Because solid organ malignancy is not suspected, CT of the body is unlikely to be helpful.

II-82. **The answer is A.** *(Chap. 108)* This patient presents with a multisystem illness involving the heart, kidneys, and peripheral nervous system. The physical examination is suggestive of amyloidosis with classic waxy papules in the folds of his body. The laboratories are remarkable for renal failure of unclear etiology with significant proteinuria but no cellular casts. A possible etiology of the renal failure is suggested by the elevated gamma globulin fraction and low hematocrit, bringing to mind a monoclonal gammopathy perhaps leading to renal failure through amyloid light-chain (AL) deposition. This could also account for the enlarged heart seen on the echocardiogram and the peripheral neuropathy. The fat-pad biopsy is generally reported to be 60–80% sensitive for amyloid; however, it would not allow a diagnosis of this patient's likely myeloma. A right heart catheterization probably would prove that the patient has restrictive cardiomyopathy secondary to amyloid deposition; however, it too would not diagnose the underlying plasma cell dyscrasia. Renal ultrasound, although warranted to rule out obstructive uropathy, would not be diagnostic. Similarly, the electromyogram and nerve conduction studies would not be diagnostic. The bone marrow biopsy is about 50–60% sensitive for amyloid, but it would allow evaluation of the percentage of plasma cells in the bone marrow and allow the diagnosis of multiple myeloma to be made. Multiple myeloma is associated with amyloid AL in approximately 20% of cases. Light chains most commonly deposit systemically in the heart, kidneys, liver, and nervous system, causing organ dysfunction. In these organs, biopsy would show the classic eosinophilic material that, when exposed to Congo red stain, has a characteristic apple-green birefringence. Extensive multisystemic involvement typifies AL amyloidosis, and the median survival period without treatment is usually only approximately 1–2 years from the time of diagnosis.

II-83. **The answer is C.** *(Chap. 108)* The most common form of familial amyloidosis is ATTRm in the updated nomenclature, caused by mutation of the abundant plasma protein transthyretin (TTR; also known as *prealbumin*). More than 100 TTR mutations are known, and most are associated with ATTR amyloidosis. One variant, V122I, has a carrier frequency that may be as high as 4% in the African American population and is associated with late-onset cardiac amyloidosis. The actual incidence and penetrance of disease in the African American population are the subject of ongoing research, but ATTR amyloidosis warrants consideration in the differential diagnosis of African American patients who present with concentric cardiac hypertrophy and evidence of diastolic dysfunction, particularly in the absence of a history of hypertension. DNA sequencing is the standard for diagnosis of ATTR. Without intervention, the survival period after onset of ATTR disease is 5–15 years. Standard treatment for heart failure with preserved ejection fraction is indicated. Orthotopic liver transplantation replaces the major source of variant TTR production with a source of normal TTR. Although liver transplantation can slow disease progression and improve chances of survival, it does not reverse sensorimotor neuropathy. Liver transplantations are most successful in young patients with early peripheral neuropathy; older patients with familial amyloidotic cardiomyopathy or advanced polyneuropathy often experience end-organ disease progression despite successful liver transplantation.

II-84. **The answer is B.** *(Chap. 110)* Posttransplant patients, particularly recipients of allogeneic transplantation, require unique approaches to the problem of infection (Figure II-84). Early after transplantation, patients are profoundly neutropenic, and because the risk of bacterial infection is so great, most centers place patients on broad-spectrum antibiotics once the granulocyte count falls to <500/μL. Early on, because of neutropenia and mucositis, patients are at risk of *Candida* infection. Prophylaxis against fungal infections

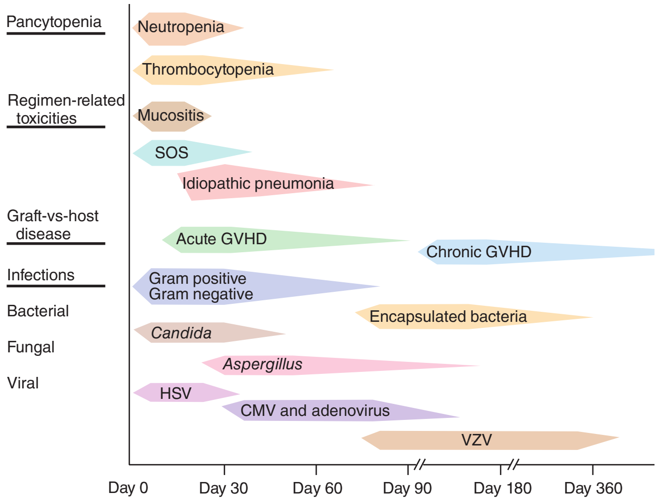


FIGURE II-84 Major syndromes complicating marrow transplantation. The size of the shaded area roughly reflects the period of risk of the complication. *Abbreviations:* CMV, cytomegalovirus; GVHD, graft-versus-host disease; HSV, herpes simplex virus; SOS, sinusoidal obstructive syndrome (formerly veno-occlusive disease); VZV, varicella-zoster virus.

reduces rates of infection and improves overall survival. Fluconazole is often used for patients with standard risk, whereas prophylaxis with mold active agents (voriconazole or posaconazole) should be considered for patients at higher risk, such as those with a prior fungal infection. Despite these prophylactic measures, most patients will develop fever and signs of infection after transplant. The other listed infections typically develop later in the course of transplant, as shown below.

II-85. The answer is B. *(Chap. 111)* Heparin-induced thrombocytopenia (HIT) is a clinical diagnosis that must not be missed because life-threatening thrombosis can occur if not treated appropriately. The cause of HIT is the formation of antibodies to the complex of heparin and platelet factor 4 (PF4). This complex is able to activate platelets, monocytes, and endothelial cells. Many patients exposed to heparin will develop antibodies to the heparin/PF4 complex, but only a few of these will progress to develop thrombocytopenia or thrombocytopenia with thrombosis (HITT). The typical patient will develop evidence of HIT 5–14 days after exposure to heparin, although it can occur within 5 days in individuals exposed to heparin within the previous approximately 100 days, as would be expected in this patient given his recent hospitalization. The nadir platelet count is typically greater than 20,000/μL. Drug-induced thrombocytopenia due to heparin differs from that seen with other drugs in two major ways: (1) the thrombocytopenia is not usually severe, with nadir counts rarely <20,000/μL and (2) HIT is not associated with bleeding and, in fact, markedly increases the risk of thrombosis.

II-86. The answer is C. *(Chap. 111)* As soon as heparin-induced thrombocytopenia (HIT) is suspected, heparin should be discontinued and replaced with an alternative form of anticoagulation to protect against development of new thromboses. Low-molecular-weight heparins (LMWHs), such as enoxaparin, are not appropriate treatment options in individuals with HIT. Although heparin is 10 times more likely to cause HIT, LMWHs also cause the illness and should not be used. The primary agents used for HIT in the United States are the direct thrombin inhibitors argatroban and lepirudin. Argatroban is the preferred agent for this patient because of his renal failure. The drug is not excreted by the kidneys, and no dosage adjustment is required. In contrast, lepirudin is markedly increased in renal failure, and significant dosage adjustment is required. Danaparoid has previously been used frequently for HIT/HITT, but this medication is no longer available in the

United States. Other anticoagulants that are used for treatment of HIT include bivalirudin and fondaparinux, but these are not currently approved by the U.S. Food and Drug Administration for this indication.

II-87. and II-88. **The answers are A and E, respectively.** *(Chap. 111)* This patient presents with the classic pentad of thrombotic thrombocytopenic purpura (TTP): fever, neurologic symptoms, acute renal failure, thrombocytopenia, and microscopic angiopathic hemolytic anemia (MAHA). The peripheral blood smear shows schistocytes and decreased platelets consistent with MAHA. Although this is the classic presentation of TTP, it is not necessary to have all five characteristics for an individual to be diagnosed with TTP. The pathogenesis of inherited and idiopathic TTP is due to a deficiency of the ADAMTS13 protein or antibodies directed against the protein. The ADAMTS13 protein is a metalloproteinase that cleaves von Willebrand factor (vWF). In the absence of ADAMTS13, ultra-large vWF multimers circulate in the blood and can cause pathogenic platelet adhesion and activation, resulting in microvascular ischemia and microangiopathic hemolytic anemia. However, it appears as if there is a necessary inciting event, because not all individuals with an inherited deficiency of ADAMTS13 develop TTP. Some drugs have been implicated as causative agents in TTP. Ticlopidine and possibly clopidogrel cause TTP by inducing antibody formation. Other drugs including mitomycin C, cyclosporine, and quinine can cause TTP by causing direct endothelial toxicity. In patients presenting with new thrombocytopenia, with or without evidence of renal insufficiency and other elements of classic TTP, laboratory data should be obtained to rule out disseminated intravascular coagulation (DIC) and to evaluate for evidence of MAHA. Findings to support the TTP diagnosis include an increased lactate dehydrogenase and indirect bilirubin, decreased haptoglobin, and increased reticulocyte count, with a negative direct antiglobulin test. The peripheral smear should be examined for evidence of schistocytes. Polychromasia is usually also present due to the increased number of young red blood cells (RBCs), and nucleated RBCs are often present, which is thought to be due to infarction in the microcirculatory system of the bone marrow. A diagnosis of TTP can be made based on clinical factors. It should be differentiated from DIC, which causes MAHA but has a predominant coagulopathy. Hemolytic uremic syndrome also causes MAHA and appears very similar to TTP in clinical presentation, although neurologic symptoms are less prominent. Often a preceding diarrheal illness alerts one to hemolytic uremic syndrome as the cause of MAHA. It is important to make a prompt and correct diagnosis as the mortality of TTP without treatment is 85–100%, decreasing to 10–30% with treatment. The primary treatment for TTP remains plasma exchange. Plasma exchange should be continued until the platelet count returns to the normal range and there is no further evidence of hemolysis for at least 2 days. Glucocorticoids can be used as adjunctive treatment in TTP, but they are not effective as the sole therapy. Additionally, other immunomodulatory therapies have been reported to be successful in refractory or relapsing TTP, including rituximab, vincristine, cyclophosphamide, and splenectomy. A significant relapse rate is noted; 25–45% of patients relapse within 30 days of initial "remission," and 12–40% of patients have late relapses. Relapses are more frequent in patients with severe ADAMTS13 deficiency at presentation.

II-89. **The answer is A.** *(Chap. 112)* Commonly used tests of hemostasis provide the initial screening for clotting factor activity, and disease phenotype often correlates with the level of clotting activity (Figure II-89). An isolated abnormal prothrombin time (PT) suggests factor VII deficiency, whereas a prolonged activated partial thromboplastin time (aPTT) indicates most commonly hemophilia or factor XI deficiency. The prolongation of both PT and aPTT suggests deficiency of factors V, X, and II, or fibrinogen abnormalities. The addition of the missing factor at a range of doses to the subject's plasma will correct the abnormal clotting times; the result is expressed as a percentage of the activity observed in normal subjects.

II-90. **The answer is B.** *(Chap. 113)* Venous thrombosis occurs through activation of the coagulation cascade primarily through the exposure to tissue factor, and the genetic factors that

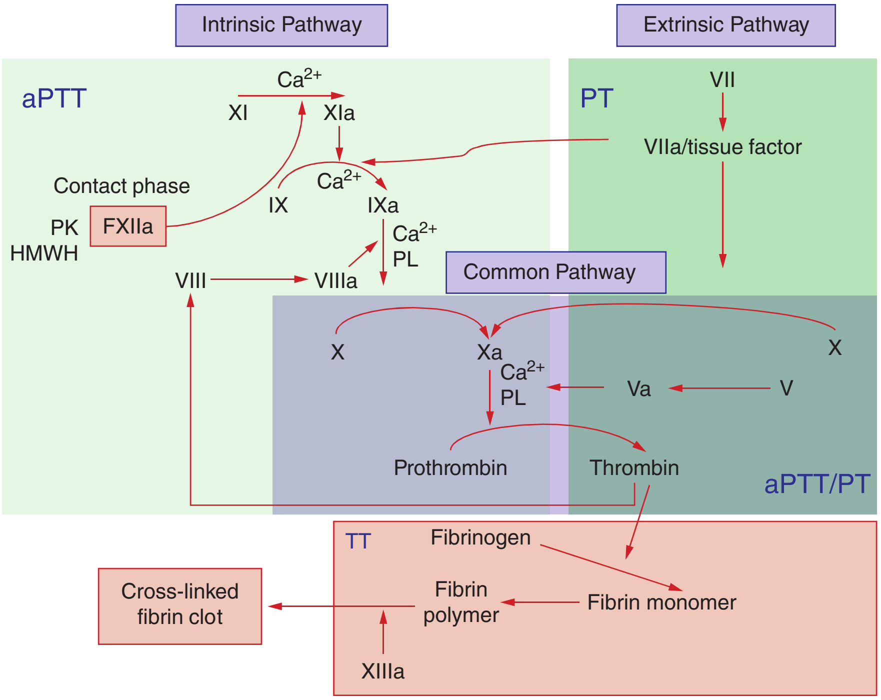


FIGURE II-89 Coagulation cascade and laboratory assessment of clotting factor deficiency by activated partial prothrombin time (aPTT), prothrombin time (PT), thrombin time (TT), and phospholipid (PL). *Abbreviations:* HMWH, high molecular-weight heparin; PK, prekallikrein.

contribute to a predisposition to venous thrombosis typically are those polymorphisms affecting procoagulant or fibrinolytic pathways. In contrast, arterial thrombosis occurs in the setting of a platelet activation, and the genetic predisposition for arterial thrombosis includes mutations that affect platelet receptors or redox enzymes. The most common inherited risk factors for venous thrombosis are the factor V Leiden mutation and the prothrombin 20210 mutation. Other mutations predisposing an individual to venous thrombosis include inherited deficiency of protein C or S and mutations of fibrinogen, tissue plasminogen activator, thrombomodulin, or plasminogen activator inhibitor. The glycoprotein Ib platelet receptor mutation would increase the risk of arterial, but not venous, thrombosis.

II-91. **The answer is A.** *(Chap. 113)* D-dimer is a degradation product of cross-linked fibrin and is elevated in conditions of ongoing thrombosis. Low concentrations of D-dimer are considered to indicate the absence of thrombosis. Patients over the age of 70 will frequently have elevated D-dimers in the absence of thrombosis, making this test less predictive of acute disease. Clinical symptoms are often not present in patients with deep venous thrombosis (DVT) and do not affect interpretation of a D-dimer. Tobacco use, while frequently considered a risk factor for DVT, and previous DVT should not affect the predictive value of D-dimer. Homan sign, calf pain elicited by dorsiflexion of the foot, is not predictive of DVT and is unrelated to D-dimer.

II-92 to II-95. **The answers are 92-C, 93-B, 94-D, 95-A.** *(Chap. 114)* Anticoagulant drugs inhibit steps in the clotting cascade (Figure II-95). Apixaban targets factor Xa to cause inhibition. Rivaroxaban and edoxaban also target factor Xa. Dabigatran, another novel oral anticoagulant, targets and inhibits thrombin. Aspirin inhibits thromboxane A_2 (TXA_2) synthesis by irreversibly acetylating cyclooxygenase-1 (COX-1). Reduced TXA_2 release attenuates platelet activation and recruitment to the site of vascular injury. Abciximab, eptifibatide, and tirofiban inhibit the final common pathway of platelet aggregation by blocking fibrinogen and von Willebrand factor binding to activated glycoprotein (Gp) IIb/IIIa. Like

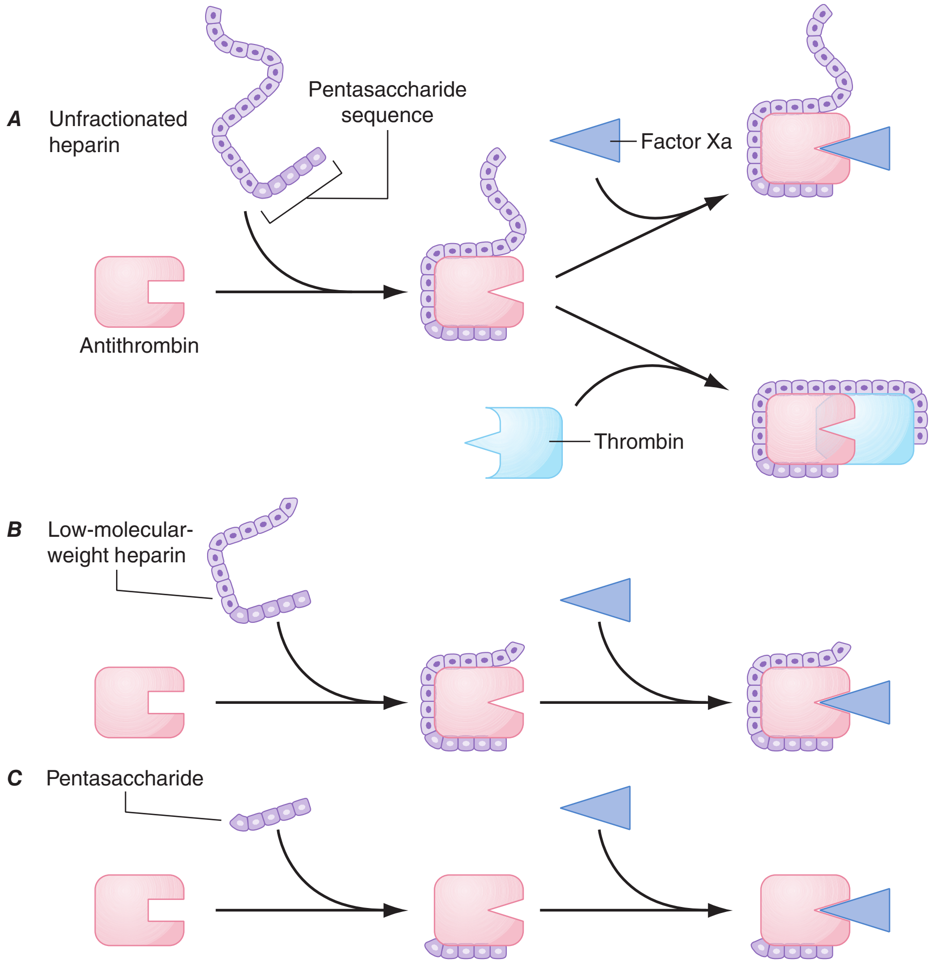
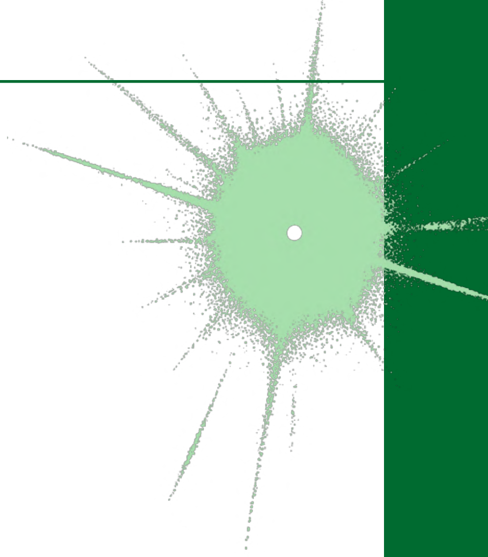


FIGURE II-95 Mechanism of action of heparin, low-molecular-weight heparin (LMWH), and fondaparinux, a synthetic pentasaccharide. ***A.*** Heparin binds to antithrombin via its pentasaccharide sequence. This induces a conformational change in the reactive center loop of antithrombin that accelerates its interaction with factor Xa. To potentiate thrombin inhibition, heparin must simultaneously bind to antithrombin and thrombin. Only heparin chains composed of at least 18 saccharide units, which correspond to a molecular weight of 5400, are of sufficient length to perform this bridging function. With a mean molecular weight of 15,000, all of the heparin chains are long enough to do this. ***B.*** LMWH has greater capacity to potentiate factor Xa inhibition by antithrombin than thrombin because, with a mean molecular weight of 4500–5000, at least half of the LMWH chains are too short to bridge antithrombin to thrombin. ***C.*** The pentasaccharide only accelerates factor Xa inhibition by antithrombin because the pentasaccharide is too short to bridge antithrombin to thrombin.

heparin, low-molecular-weight heparin (LMWH) exerts its anticoagulant activity by activating antithrombin. With a mean molecular weight of 5000, which corresponds to about 17 saccharide units, at least half of the pentasaccharide-containing chains of LMWH are too short to bridge thrombin to antithrombin.

SECTION III

Infectious Diseases



QUESTIONS

DIRECTIONS: Choose the one best response to each question.

III-1. All of the following statements regarding global infectious diseases are true EXCEPT:

A. Drug-resistant tuberculosis is common in the former Soviet bloc countries
B. Infectious diseases are the leading cause of death worldwide.
C. As of 2013 over 50% of deaths in sub-Saharan Africa were related to infectious diseases.
D. The absolute number of infectious disease–related deaths has remained relatively constant in the past 25 years.
E. The rate of infectious disease–related death has dropped notably in the past 25 years.

III-2. Which of the following infectious organisms is most likely to cause relative bradycardia during a febrile event?

A. *Pseudomonas aeruginosa*
B. *Salmonella typhi*
C. *Staphylococcus aureus*
D. *Streptococcus pneumoniae*
E. *Streptococcus pyogenes*

III-3. All of the following statements regarding the relationship between the world's interconnectedness and the spread of infectious diseases are true, EXCEPT:

A. Human migration has been the major source of epidemics.
B. Travelers contribute to the worldwide spread of multidrug-resistant organisms.
C. The 1918 influenza pandemic (Spanish flu) spread primarily through increasing train travel across the globe.
D. Native American populations were devastated by imported diseases brought by European explorers.
E. Travelers have been implicated in introducing vector-borne infections to new geographic areas.

III-4. All of the following statements regarding the human microbiome are true, EXCEPT:

A. Indigenous microbial organisms living in close association with humans modulate the ability of pathogens to establish themselves on host surfaces.
B. The human microbiome may impact obesity; type 1 diabetes; cognition; neurologic states; autoimmune diseases; and skin, gastrointestinal, respiratory, and vaginal infectious diseases.
C. The use of fecal transplants is an important way to treat and prevent recurrences of serious *Clostridium difficile* infection.
D. There is a high level of variability between individuals' microbiome components in an individual over that person's life span.
E. Use of antibiotics may disrupt the microbiome and may impact the progression of infection.

III-5. A 42-year-old man has a history of splenectomy following trauma at the age of 20. He received appropriate vaccinations immediately after his trauma but has not had any medical care for more than 10 years. He is homeless. He presents to the emergency department with a fever of 102.3°F (39.1°C), blood pressure of 70/40, heart rate of 130 beats/min respiratory rate of 30 breaths/min, and oxygen saturation of 95% on room air. What is the best initial antibiotic therapy for this patient?

A. Ceftriaxone and vancomycin
B. Ceftriaxone, ampicillin, and vancomycin
C. Ceftriaxone, vancomycin, and amphotericin B
D. Clindamycin, gentamicin, and vancomycin
E. Clindamycin and quinine

III-6. The patient in question III-5 subsequently develops multisystem organ failure due to overwhelming sepsis and dies despite appropriate medical management. Which of the following organisms would be *most* likely to cause the patient's presentation?

A. *Escherichia coli*
B. *Haemophilus influenzae*
C. *Neisseria meningitidis*
D. *Pseudomonas aeruginosa*
E. *Streptococcus pneumoniae*

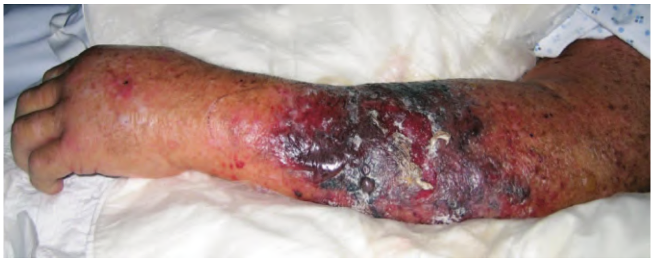


FIGURE III-7

III-7. A 44-year-old woman with relapsed acute myelogenous leukemia has undergone a myeloablative allogeneic stem cell transplantation. She has been profoundly neutropenic for 21 days and has had a persistent fever for the past 7 days. Today, she has appeared septic with hypotension, tachycardia, and a new oxygen requirement. A nurse calls you to evaluate a new rash. On examination, the patient looks ill. She is tachypneic and is rigoring. Skin examination reveals a few scattered areas of hemorrhagic vesicles, the largest measuring 3 cm in diameter, on the hands and legs (Figure III-7). What is the most likely causative organism?

A. *Neisseria meningitidis*
B. *Pseudomonas aeruginosa*
C. *Rickettsia rickettsii*
D. *Staphylococcus aureus*
E. *Vibrio vulnificus*

III-8. A 63-year-old male with a past medical history of alcoholic cirrhosis presented with 3 days of right calf pain, chills, fevers, malaise, and a bullous rash on the right lower extremity after a meal of crab cakes and oysters (Figure III-8). He presents to the emergency department with a fever of 39.1°C (102.3°F), blood pressure of 85/50, heart rate of 130 beats/min, respiratory rate of 30 breaths/min, and oxygen saturation of 95% on room air. What antibiotics should you initiate?

A. Ceftriaxone
B. Doxycycline and ceftriaxone
C. Moxifloxacin
D. Trimethoprim/sulfamethoxazole
E. Vancomycin

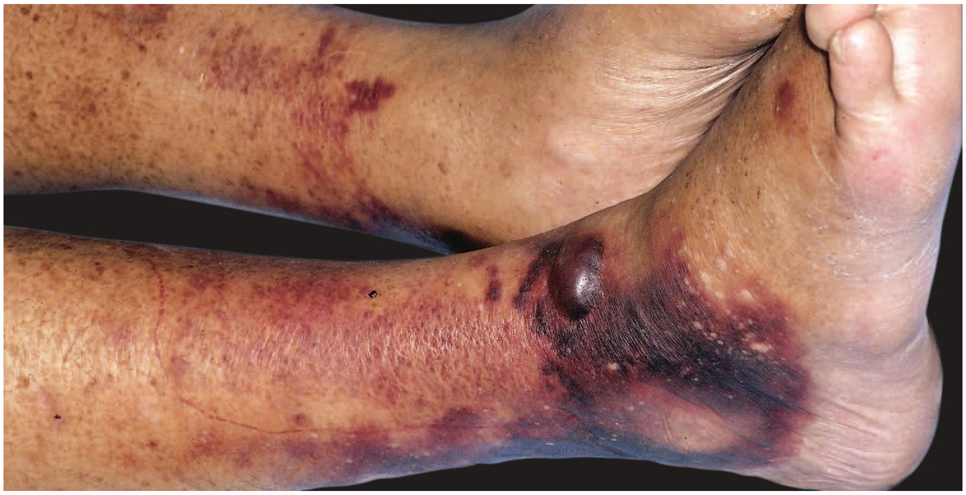


FIGURE III-8 Reproduced with permission from Wolff K et al: *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology*, 8th ed. New York: McGraw Hill, 2017.

III-9. A 56-year-old woman who is 1 week postoperative right total knee replacement presents with fever and severe pain at the incision site. She is treated empirically with cefazolin for cellulitis. The admitting team notes that the degree of pain is disproportionate to the amount of cellulitis. She then develops septic shock complicated by hypotension and evidence of disseminated intravascular coagulation. A CT scan of her abdomen demonstrates a collection of fluid with gas in the deep fascia of her right leg. Emergent surgery is planned. What changes to the patient's antibiotic therapy should be recommended?

A. Continue cefazolin and add clindamycin
B. Continue cefazolin and add clindamycin and gentamicin
C. Discontinue cefazolin and add clindamycin, vancomycin, and ampicillin-sulbactam
D. Discontinue cefazolin and add ampicillin-sulbactam and vancomycin
E. Discontinue cefazolin and add vancomycin and gentamicin

III-10. According to the Centers for Disease Control and Prevention, in the United States between 2012 and 2019 the number of reported cases of measles increased from 55 to 1282. Which of the following factors is the most likely initial source of measles infection in this growing outbreak in the United States?

A. Indigenous transmission from unvaccinated individuals
B. Importation of the disease from an endemic area
C. Spontaneous mutation of measles vaccine virus to a virulent form
D. Spontaneous outbreak from an environmental source

III-11. Regarding the growing U.S. measles outbreak described in question III-10, once the measles infection was established in the United States, what was the source of sustained transmission?

A. Transmission of disease among individuals too young to undergo vaccination
B. Transmission of disease among individuals who had chosen to forego vaccination for personal or religious reasons
C. Transmission of disease among individuals with medical contraindications
D. Transmission of disease among unvaccinated foreign travelers
E. Viral breakthrough in vaccinated individuals

III-12. A 63-year-old man has chronic obstructive pulmonary disease and presents to your office for routine follow-up. He has no complaints currently and feels well. His most recent FEV_1 was 55% predicted, and he is not on oxygen. He received one dose of pneumococcal vaccine 7 years previously. He is asking whether he should receive another dose of pneumococcal vaccine. According to the guidelines of the Centers for Disease Control and Prevention, what is your recommendation?

A. He does not require further vaccination unless his FEV_1 drops below 50% predicted.
B. He does not require further vaccination until he reaches age 65.
C. He should be revaccinated today.
D. He should be revaccinated 10 years after his initial vaccine.
E. No further vaccination is recommended as a single dose is all that is required.

III-13. In which of the following patients is the vaccine listed the LEAST indicated?

A. A 35-year-old woman who has never had varicella zoster infection and is 12 weeks pregnant with her first child: varicella vaccine
B. A 23-year-old woman with a past medical history of asthma and is 20 weeks pregnant with her second child: influenza vaccine
C. A 32-year-old woman who is 25 weeks pregnant with her second child and has received all recommended vaccines one year ago: tetanus/diphtheria/pertussis
D. A 26-year-old woman 2 weeks postpartum with her second child whom she is breastfeeding: measles/mumps/rubella
E. A 21-year-old woman who is 30 weeks pregnant with her first child and has a low-grade fever and an upper respiratory tract infection: hepatitis A vaccine

III-14. Which of the following immunizations is required for entry into many countries in sub-Saharan Africa?

A. Cholera
B. Hepatitis A
C. Meningococcus
D. Typhoid fever
E. Yellow fever

III-15. A 48-year-old woman is traveling to Kenya for a safari. She has no past medical history and is not taking any other medications. All of the following may be recommended for prophylaxis against malaria for this patient EXCEPT:

A. Atovaquone-proguanil
B. Chloroquine
C. Doxycycline
D. Mefloquine

III-16. A 28-year-old man with no past medical history is traveling to Haiti with a religious organization for a service project. You should offer him all of the following treatments and guidance advice EXCEPT:

A. Malaria prophylaxis with chloroquine
B. Recommend use of oil of lemon eucalyptus
C. Recommend use of diethyltoluamide (DEET)-containing insect repellents with a concentration of 50%
D. Pneumococcal vaccine
E. Vaccination for hepatitis A

III-17. In which of the following manners are infectious diseases expected to change due to climate change?

A. Climate change may increase the likelihood that malaria will spread in subtropical and temperate regions of the Americas.
B. Increased mosquito-biting rates may lead to an increased likelihood of acquiring malaria.
C. The primary tick vector for Lyme disease, anaplasmosis, and babesiosis will spread to southern Canada by the end of the century.
D. To mitigate the worst impacts of climate change on infectious diseases, countries have agreed to limit warming to less than 2°C by 2050.
E. All of the above are true.

III-18. Which of the following bacteria are a common cause of community-acquired pneumonia in hospitalized patients but not in patients treated as outpatients?

A. *Chlamydia pneumoniae*
B. *Haemophilus influenzae*
C. *Legionella* species
D. *Mycoplasma pneumoniae*
E. *Streptococcus pneumoniae*

III-19. A 55-year-old man presents to his primary care physician with a 2-day history of cough and fever. His cough is productive of thick dark green sputum. His past medical history is significant for hypercholesterolemia treated with rosuvastatin. He does not smoke cigarettes and is generally quite healthy, exercising several times weekly. He has no ill contacts and cannot recall the last time he was treated with any antibiotics. On presentation, his vital signs are temperature 38.9°C (102.1°F), blood pressure 132/78, heart rate 87 beats/min, respiratory rate 20 breaths/min, and SaO_2 95% on room air. Crackles are present in the right lung base, as is egophony. A chest radiograph demonstrates segmental consolidation of the right lower lobe with air bronchograms. What is the most appropriate approach to the ongoing care of this patient?

A. Obtain a sputum culture and await results prior to initiating treatment.
B. Perform a chest CT to rule out postobstructive pneumonia.
C. Refer to the emergency department for admission and treatment with IV antibiotics.
D. Treat with amoxicillin.
E. Treat with moxifloxacin.

III-20. A 65-year-old woman was admitted to the intensive care unit for management of septic shock associated with an infected hemodialysis catheter. She was initially intubated on hospital day 1 with acute respiratory distress syndrome. She had slowly been improving such that her FiO_2 had been weaned to 0.40, and she was no longer febrile or requiring vasopressors. On hospital day 7, however, she developed a new fever to 39.4°C (102.9°F) with increased thick yellow-green sputum in her endotracheal tube. You suspect the patient has ventilator-associated pneumonia (VAP). Which of the following makes the most definitive diagnosis of VAP in this patient?

A. An endotracheal aspirate yielding a new organism typical of VAP
B. Quantitative cultures from an endotracheal aspirate yielding more than 10^6 organisms typical of VAP
C. Quantitative culture from a protected brush specimen yielding more than 10^3 organisms typical of VAP
D. The presence of a new infiltrate on chest radiograph
E. There is no single set of criteria that is reliably diagnostic of pneumonia in a ventilated patient.

III-21. You admit a patient with severe community-acquired pneumonia who requires intubation and mechanical ventilation. She has decreased breath sounds and dullness to percussion halfway up her right lung. Chest x-ray and ultrasound confirm the presence of a large pleural effusion. You perform a diagnostic thoracentesis, but fluid remains. All of the following are indications for complete drainage of the pleural fluid EXCEPT:

A. Pleural fluid pH <7
B. Pleural fluid glucose <2.2 mmol/L
C. Pleural fluid protein >5 g/dL
D. Pleural fluid lactate dehydrogenase concentration >1000 units/L
E. Bacteria seen or cultured from pleural fluid

III-22. For how many days should uncomplicated community-acquired pneumonia typically be treated?

A. 3 days
B. 5 days
C. 7 days
D. 10 days
E. 14 days

III-23. All of the following statements regarding lung abscesses are true EXCEPT:

A. Posterior upper lobes and superior lower lobes are the most common locations of primary lung abscesses.
B. Primary lung abscesses are often caused by anaerobic bacteria.
C. Primary lung abscesses can be treated with IV ampicillin-sulbactam.
D. Surgical intervention should be considered for lung abscesses with cavity sizes >2cm
E. The major risk factor for primary lung abscesses is oropharyngeal aspiration.

III-24. A 50-year-old man is admitted to the hospital with 3 weeks of progressive malaise, weight loss, and purulent cough. He has a history of alcoholism and frequent emergency department visits due to intoxication. He is a former subprime mortgage broker who is now unemployed and lives with his elderly parents. On examination, he appears disheveled and chronically ill. His temperature is 38.5°C, heart rate is 110 beats/min, blood pressure is 110/65, and respiratory rate is 18 breaths/min, with room air SaO_2 of 93%. He has extremely poor dentition, is coughing up foul-smelling phlegm, and has rhonchi over his right lung base. There is no diffuse adenopathy, and the only other remarkable finding is an enlarged liver. His chest radiograph is shown in Figure III-24. Which of the following is the most appropriate therapy?

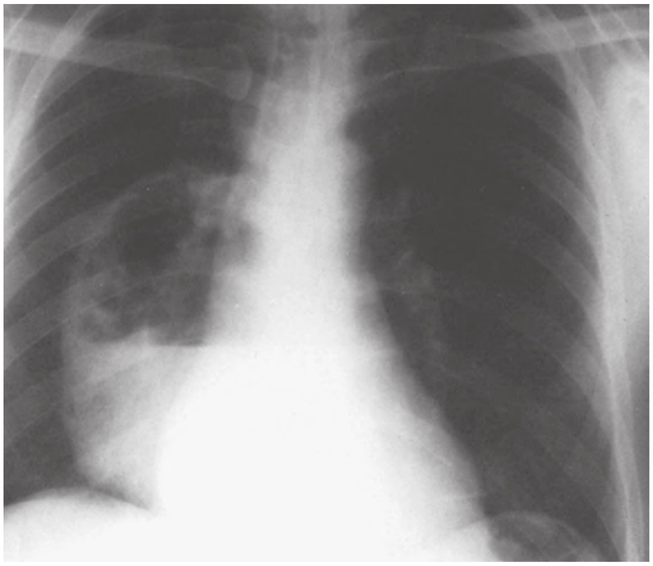


FIGURE III-24 Reproduced with permission from Mandell GL: *Atlas of Infectious Diseases*, Vol VI. Philadelphia: Current Medicine Inc, Churchill Livingstone, 1996.

A. Ampicillin-sulbactam
B. Aztreonam
C. Metronidazole
D. Micafungin
E. Penicillin

III-25. Which of the following organisms is the most common cause of noninjection drug use–related native valve infective endocarditis in the community?

A. Coagulase-negative staphylococci
B. Coagulase-positive staphylococci
C. Enterococci
D. *Pseudomonas*
E. Non-enterococcal streptococci

III-26. All of the following are minor criteria in the Modified Duke Criteria for the clinical diagnosis of infective endocarditis EXCEPT:

A. Immunologic phenomena (glomerulonephritis, Osler nodes, Roth spots)
B. New valvular regurgitation on transthoracic echocardiogram
C. Predisposing condition (heart condition, IV drug use)
D. Temperature >38°C
E. Vascular phenomena (e.g., arterial emboli, septic pulmonary emboli, Janeway lesions)

III-27. Which of the following patients should receive antibiotic prophylaxis prior to prevent infective endocarditis?

A. A 62-year-old woman with a history of a prosthetic mitral valve undergoing colonoscopy
B. A 32-year-old man with a history of mitral valve endocarditis undergoing a routine dental cleaning
C. A 65-year-old man with a history of mitral valve endocarditis undergoing a cystoscopy
D. A 41-year-old woman with known mitral valve prolapse having a tooth cavity filled
E. A 70-year-old man with a history of aortic valve replacement 2 years prior undergoing gingival surgery

III-28. A 38-year-old homeless man presents to the emergency department with a transient ischemic attack characterized by a facial droop and left arm weakness lasting 20 min and left upper quadrant pain. He reports intermittent subjective fevers, diaphoresis, and chills for the past 2 weeks. He has had no recent travel or contact with animals. He has no recent history of taking antibiotics. Physical examination reveals a slightly distressed man with disheveled appearance. His temperature is 38.2°C, heart rate is 90 beats/min, and blood pressure is 127/74. He has poor dentition. Cardiac examination reveals an early diastolic murmur over the left third intercostal space. His spleen is tender and 2 cm descended below the costal margin. He has tender, painful red nodules on the tips of the third finger of his right hand and on the fourth finger of his left hand that are new. He has nits evident on his clothes, consistent with body louse infection. White blood cell count is 14,500, with 5% band forms and 93% polymorphonuclear cells. Blood cultures are drawn followed by empirical vancomycin therapy. These cultures remain negative for growth 5 days later. He remains febrile but hemodynamically stable but does develop a new lesion on his toe similar to those on his fingers on hospital day 3. A transthoracic echocardiogram reveals a 1-cm mobile vegetation on the cusp of his aortic valve and moderate aortic regurgitation. A CT scan of the abdomen shows an enlarged spleen with wedge-shaped splenic and renal infarctions. What test should be sent to confirm the most likely diagnosis?

A. *Bartonella* serology
B. Epstein-Barr virus heterophile antibody
C. HIV polymerase chain reaction
D. Peripheral blood smear
E. Q fever serology

III-29. In a patient with bacterial endocarditis, which of the following echocardiographic lesions is most likely to lead to embolization?

A. 5-mm mitral valve vegetation
B. 5-mm tricuspid valve vegetation
C. 11-mm aortic valve vegetation
D. 11-mm mitral valve vegetation
E. 11-mm tricuspid valve vegetation

III-30. All of the following infectious clinical syndromes typically cause bullous lesions EXCEPT:

A. Scalded skin syndrome
B. Necrotizing fasciitis
C. Varicella
D. *Vibrio* infection
E. Gas gangrene

III-31. A 49-year-old man with a history of alcoholism is admitted to the hospital with sepsis syndrome. He is somnolent, febrile to 40°C, hypotensive, and tachycardic. His room air oxygen saturation is 95% on nasal oxygen. He is disheveled with multiple skin excoriations on his arms, legs, and trunk. There is tenderness and swelling over his left chest but no other focal findings. Laboratory studies and blood cultures are pending. After receiving fluids, vasopressors, and empiric antibiotics, a chest CT is performed and shown in Figure III-31. Which of the following is the most likely causative organism?

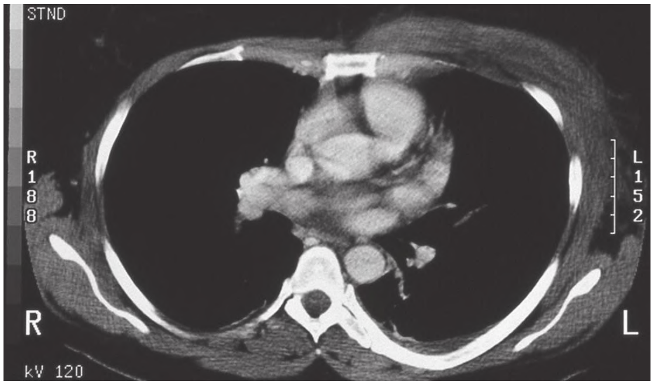


FIGURE III-31

A. *Actinomyces israelii*
B. *Klebsiella pneumoniae*
C. Oral anaerobic bacteria
D. *Streptococcus pneumoniae*
E. *Streptococcus pyogenes*

III-32. A 76-year-old woman presents with 3 days of fever and 1 day of severe pain in her left knee to the point where she can no longer stand. She has no past medical history. She is not sexually active. On examination, her temperature is 38.3°C. Her heart rate is 100 beats/min, with blood pressure of 128/75. Her left knee is tender, with erythema and a palpable effusion. Her cardiac, lung, and abdominal examinations are all normal. Which of the following should you do?

A. Draw blood cultures and perform joint aspiration.
B. Draw blood cultures, perform an x-ray of the left knee, and initiate vancomycin.
C. Draw blood cultures, perform joint aspiration, and initiate vancomycin.
D. Initiate vancomycin and perform an x-ray of the left knee.
E. Perform joint aspiration and initiate ceftriaxone.

III-33. A 56-year-old man with a past medical history of hypertension presents with 3 days of severe lower back pain and a temperature of 38.0°C. He has no surgical history. On examination, he has a temperature of 37.9°C, blood pressure of 133/81, heart rate of 95 beats/min, and normal respirations. His physical examination is notable for severe tenderness at L2. He has normal strength, sensation, and reflexes in his legs. Initial labs show a white blood cell count of 8.0 cells/mm^3 and an absolute neutrophil count of 5.0 cells/mm^3. C-reactive protein is elevated to 31, and erythrocyte sedimentation rate is 100 mm/h. What should your next steps include?

A. Draw blood cultures and initiate vancomycin and ceftriaxone.
B. Draw blood cultures and order MRI of spine.
C. Draw blood cultures, order lumbar spine x-ray, and initiate vancomycin.
D. Draw blood cultures, order MRI of spine, and initiate vancomycin.
E. Order MRI of spine and initiate vancomycin plus ceftriaxone.

III-34. A 67-year-old woman with a history of right knee replacement 4 years prior presents with 1 month of worsening right knee pain and decreased range of motion in that knee. On examination, she is afebrile. Her right knee is warm and appears as shown in Figure III-34. She has a C-reactive protein of 13 mg/L and an erythrocyte sedimentation rate of 50 mm/h.

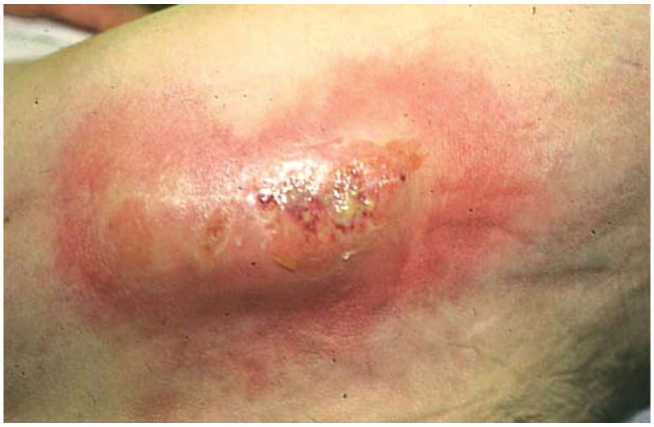


FIGURE III-34

Which of the following should you request?

A. Initiate IV vancomycin
B. Joint aspiration
C. Surgical consultation
D. A and C
E. B and C

III-35. A 45-year-old man with a history of alcoholism and presumed cirrhosis is brought to the emergency department by his friend complaining of 2–3 days of increasing lethargy and confusion. He has not consumed alcohol in the past 2 years. He currently takes no medications and works at home as a video game designer. He has no risk factors for HIV. He was referred by his primary care physician for a liver transplant evaluation and is scheduled to begin his evaluation next month. His vital signs are as follows: blood pressure (BP) 90/60, heart rate (HR) 105 beats/min, temperature 38.5°C, respiratory rate 10 breaths/min, and SaO_2 97% on room air. He is somnolent but is able to answer questions accurately. His skin is notable for many spider telangiectasias and palmar erythema. He has a distended diffusely tender abdomen with a positive fluid wave. Paracentesis reveals slightly cloudy fluid with white blood cell count of 1000/μL and 40% neutrophils. His BP increases to 100/65, and his HR decreases to 95 beats/min after 1 L of IV fluids. Which of the following statements regarding his condition and treatment is true?

A. Fever is present in >50% of cases.
B. Initial empiric therapy should include metronidazole or clindamycin for anaerobes.
C. The diagnosis of primary (spontaneous) bacterial peritonitis is not confirmed because the percentage of neutrophils in the peritoneal fluid is <50%.
D. The most likely causative organism for his condition is *Enterococcus*.
E. The yield of peritoneal fluid cultures for diagnosis is >90%.

III-36. A 48-year-old woman with a history of end-stage renal disease due to diabetic renal disease is admitted to the hospital with 1 day of abdominal pain and fever. She has been on continuous ambulatory peritoneal dialysis for the last 6 months. She reports that for the last day she has had poor return of dialysate and is feeling bloated. She has had complications from her diabetes including retinopathy and peripheral neuropathy. She is uncomfortable but not toxic. Her vital signs include the following: temperature 38.8°C, blood pressure 130/65, heart rate 105 beats/min, respiratory rate 15 breaths/min, and room air SaO_2 98%. Her abdomen is slightly distended and diffusely tender with rebound tenderness. A sample of dialysate reveals white blood cell count of 400/μL with 80% neutrophils. Empiric intraperitoneal antibiotic therapy should include which of the following?

A. Cefoxitin
B. Fluconazole
C. Metronidazole
D. Vancomycin
E. Voriconazole

III-37. A 59-year-old man presents to the hospital with 5 days of fever, chills, nausea, and right upper quadrant pain. His temperature is 39°C, and he appears toxic. His blood pressure is 110/70, heart rate is 110 beats/min, and respiratory rate is 18 breaths/min with room air SaO_2 of 96%. He has diminished breath sounds at the right base and diffuse tenderness in the right upper quadrant. He has a history of choledocholithiasis that has gone untreated. His CT scan of the abdomen is shown in Figure III-37A. Which of the following statements about his condition is true?

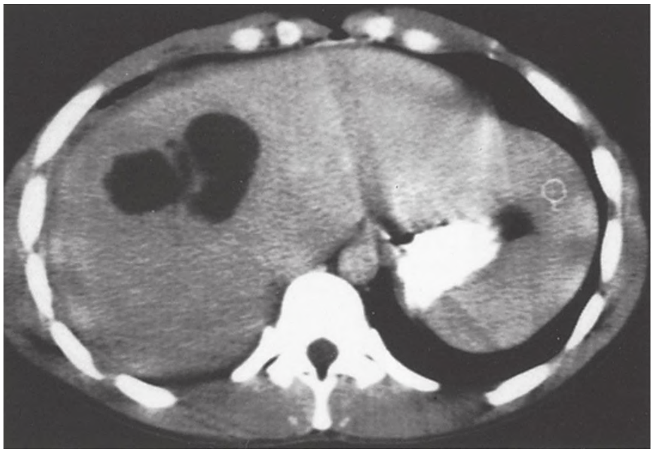


FIGURE III-37A Reproduced with permission from Lorber B: *Atlas of Infectious Diseases, Vol VII: Intra-Abdominal Infections, Hepatitis, and Gastroenteritis*. Philadelphia: Current Medicine, 1996.

A. Concomitant bacteremia is rare (<10%).
B. He should receive empiric antibiotics targeting *Candida* species.
C. He should receive empiric antibiotics targeting anaerobic organisms.
D. He should undergo percutaneous drainage.
E. His serum alkaline phosphatase is most likely normal.

III-38. A 52-year-old woman with a past medical history of hypertension presents to her primary care doctor prior to a 2-week long mission trip her church is taking to Guatemala. You provide her with extensive pretravel counseling and treatment. You could provide her with all of the following guidance and prophylaxis regarding the prevention of traveler's diarrhea EXCEPT:

A. Avoid raw vegetables, salads, and unpeeled fruit.
B. Take bismuth subsalicylate.
C. Take ciprofloxacin.
D. Take probiotics.
E. Take rifaximin.

III-39. A 78-year-old woman presents to the hospital from her nursing home with complaints of diarrhea. She has been in the nursing home for the past 5 years following a stroke with residual right-sided hemiplegia. She was recently treated with ceftriaxone for pyelonephritis due to *Escherichia coli*. Yesterday, she developed a temperature of 38°C (100.6°F) with a complaint of diffuse abdominal pain. Over the past 24 hours, she has had worsening abdominal pain and abdominal distention. In addition, she has had eight bowel movements. The bowel movements are loose and have become bloody. Six months ago, she was treated with oral metronidazole for a documented *Clostridium difficile* infection. Additionally, her past medical history is significant for cerebrovascular disease, atrial fibrillation, coronary artery disease requiring angioplasty, hypertension, and hyperlipidemia. On presentation to the hospital, she appears uncomfortable and has a temperature of 38.4°C (101.2°F). Her blood pressure is 98/60 and heart rate is 115 beats/min. Her abdomen appears distended and tympanitic with diffuse tenderness to palpation. An abdominal x-ray shows distention of the colon with ileus. Initial laboratory examination shows a white blood cell count of 27,200/μL with 92% neutrophils and 3% band forms. Her hemoglobin is 9.2 g/dL and hematocrit is 28.1%. One month ago, her hemoglobin was 10.1 g/dL. Given her recent antibiotic use, you consider the possibility of *C. difficile* infection. Which of the following findings is most unlikely to be found in *C. difficile* infection?

A. Bloody diarrhea
B. Fever
C. Ileus
D. Leukocytosis
E. Recurrence after therapy

III-40. In the case in question III-39, how would you treat this patient?

A. Oral metronidazole
B. IV metronidazole
C. Rectal installation of vancomycin
D. Oral vancomycin and IV metronidazole
E. Oral vancomycin

III-41. All of the following patients should be treated for *Clostridium difficile* infection EXCEPT:

A. A 57-year-old nursing home resident with diarrhea for 2 weeks and pseudomembranes found on colonoscopy with no evidence of toxin A or B in the stool
B. A 63-year-old woman with fever, leukocytosis, adynamic ileus, and a positive polymerase chain reaction for *C. difficile* in the stool
C. A 68-year-old woman with recent course of antibiotics admitted to the medical intensive care unit after presentation to the emergency department with abdominal pain and diarrhea; she was found to have severe abdominal tenderness with absent bowel sounds, systemic hypotension, and colonic wall thickening on CT of the abdomen
D. A 75-year-old woman who completed therapy with amoxicillin for an upper respiratory tract infection yesterday and now has had two loose bowel movements per day for the last 3 days; she is afebrile and has a white blood cell count of 8600/μL

III-42. An 82-year-old woman with dementia has been living in a nursing home for 5 years. She was seen by her primary care provider for evaluation of diarrhea 4 weeks ago. At that time, a stool sample was positive by polymerase chain reaction (PCR) for *Clostridium difficile*, and she was treated with oral metronidazole with some improvement in her symptoms. However, she has had five loose bowel movements per day starting 4 days ago and now has abdominal tenderness. Stool PCR remains positive. Which of the following is the most appropriate therapy?

A. Fecal microbiota transplantation
B. IVIg
C. Oral metronidazole
D. Oral nitazoxanide
E. Oral vancomycin

III-43. Which of the following antibiotics has the weakest association with the development of *Clostridium difficile*–associated disease?

A. Ceftriaxone
B. Ciprofloxacin
C. Clindamycin
D. Moxifloxacin
E. Piperacillin-tazobactam

III-44. Which of the following statements regarding the epidemiology of and risk factors for urinary tract infections (UTIs) is true?

A. About one-third of all women will experience at least one UTI in their lifetime.
B. Across all ages, UTI is two to three times more common among females.
C. Asymptomatic bacteriuria is a common and incidental finding in pregnancy that does not require treatment.
D. Contrary to popular wisdom, sexual intercourse is not a risk factor for UTI.
E. In infancy, UTI is more common among males than females.

III-45. A 30-year-old woman is admitted to the intensive care unit with a temperature of 39°C, back pain, and blood pressure of 80/50. She started feeling ill 2 days prior with increased urinary urgency and frequency, then severe right upper back pain the day prior. She has been experiencing persistent nausea and vomiting. She has a past medical history of type 1 diabetes mellitus, which is well controlled with insulin glargine and aspartate, and her fingerstick blood glucose read "high." On examination, her blood pressure was 80/50 which came up slightly to 90/60 with 2 L of normal saline, and her heart rate was 120. She appeared uncomfortable with dry mucous membranes. Her examination was normal including her abdomen, but she had severe right costovertebral angle pain on percussion. She had an anion gap metabolic acidosis, a blood urea nitrogen of 60, and a creatinine of 2.0. Urinalysis has too numerous to count bacteria with 200 white blood cells per high-powered-field. Which of the following is the best initial therapy for this patient?

A. IV ceftriaxone
B. IV Meropenem
C. IV piperacillin-tazobactam
D. Oral ciprofloxacin
E. Oral trimethoprim-sulfamethoxazole

III-46. A 23-year-old woman is seen for routine follow-up of an uncomplicated pregnancy. She had one prior visit at 10 weeks when the pregnancy was confirmed. She is currently at week 16. What is the recommendation for screening and treatment of asymptomatic bacteriuria in this patient?

A. She should be screened and treated in the third trimester only.
B. She should be screened at this time with a urine culture but not treated unless symptomatic.
C. She should be screened at this time and treated if the culture is positive.
D. She should be screened now and again in the third trimester. Treatment is recommended only if both cultures are positive.
E. She should not be screened unless she has comorbid medical conditions that increase the risk of UTI.

III-47. A 70-year-old man presents with urinary urgency, frequency, dysuria, subjective fevers, and perineal pain for 2 days. He has a past medical history of benign prostatic hypertrophy but is not currently on treatment. He had noticed a decreased urine stream for several months prior to this episode. On rectal examination, his prostate is warm, edematous, and tender to palpation. He has not been sexually active in 10 years. Urinalysis has too numerous to count bacteria with 200 white blood cells per high-powered field. A urine culture is obtained and shows $>1 \times 10^5$ of pan-sensitive *Escherichia coli*. How should you treat this patient?

A. Oral ciprofloxacin for 2 weeks
B. Oral ciprofloxacin for 4 weeks
C. Oral ciprofloxacin for 6 weeks
D. Oral trimethoprim-sulfamethoxazole for 1 week
E. Oral trimethoprim-sulfamethoxazole for 4 weeks

III-48. All of the following are common causes of urethritis in men EXCEPT:

A. *Gardnerella vaginalis*
B. *Mycoplasma genitalium*
C. *Neisseria gonorrhoeae*
D. *Trichomonas vaginalis*
E. *Ureaplasma urealyticum*

III-49. A 25-year-old woman presents with 2 days of urinary frequency, urgency, and pelvic discomfort. She has no pain in her vulva on urination. She has no other medical problems and does not have fevers. She is sexually active. A microscopic examination of her urine shows pyuria but no pathogens. After 24 hours, her urine culture does not grow any pathogens. Which of the following tests will likely confirm her diagnosis?

A. Cervical culture
B. Clue cells on microscopy of vaginal secretions
C. Nucleic acid amplification test of urine for *Chlamydia trachomatis*
D. Physical examination of the vulva and vagina
E. Vaginal pH ≥5.0

III-50. Which of the following diagnostic features characterizes bacterial vaginosis?

A. Scant vaginal secretions, erythema of vaginal epithelium, and clue cells
B. Vaginal fluid pH >4.5, clue cells, and profuse mixed microbiota on microscopic examination
C. Vaginal fluid pH >4.5, motile trichomonads on microscopic examination, and fishy odor with 10% KOH
D. Vaginal fluid pH <4.5, lactobacilli predominate on microscopic examination, and scant clear secretions
E. Vaginal fluid pH <4.5, clue cells, and profuse mixed microbiota on microscopic examination

III-51. Which of the following tests is the most sensitive to make the appropriate diagnosis in a woman seen at a sexually transmitted disease clinic with profuse, yellow, and purulent, homogenous vaginal discharge with vulvar irritation?

A. Culture
B. Enzyme-linked immunosorbent assay testing
C. Gram stain
D. Nucleic acid amplification test
E. Wet prep or saline microscopy

III-52. A 19-year-old woman is seen in the emergency department for pelvic pain. She reports 1 week of pain but has developed more severe pain on the right side of her lower abdomen over the past day with accompanying fever. Additionally, she reports pain in her right upper abdomen for the last day that is worsened by deep breathing. She is sexually active with multiple partners and only reports a past medical history of asthma. Examination is notable for fever, normal breath sounds, mild tachycardia, and a tender right upper quadrant without rebound, guarding, or masses. Pelvic examination shows a normal cervical appearance, but cervical motion tenderness and adnexal tenderness are present. No masses are palpated. A urine pregnancy test is negative and leukocytosis is present; otherwise, renal and liver function labs are normal. Which of the following is true regarding her right upper quadrant tenderness?

A. CT imaging of the abdomen would likely show diverticulitis.
B. Laparoscopic examination would show inflammation of her liver capsule.
C. She requires a surgery consult to manage acute cholecystitis.
D. The diagnosis could be made by sending hepatitis A serologies.
E. The diagnosis should be made by sending a fluorescent treponemal antibody absorbed test.

III-53. A 23-year-old college student is seen in the student health clinic for evaluation of multiple genital ulcers that he noted developing over the past week. They started as pustules and, after suppuration, are now ulcers. The ulcers are extremely tender and occasionally bleed. Examination shows multiple bilateral deep ulcers with purulent bases on the penis that bleed easily. They are exquisitely tender but are soft to palpation. Which of the following organisms is likely to be found on culture of the lesions?

A. *Haemophilus ducreyi*
B. Herpes simplex virus
C. HIV
D. *Neisseria gonorrhoeae*
E. *Treponema pallidum*

III-54. A 20-year-old female college student with no past medical history presents with 3 days of fever, headache, and agitation. On presentation to the emergency department, she experiences a seizure. On examination, she has a blood pressure of 120/70, heart rate of 90 beats/min, and respiratory rate of 16 breaths/min. Her temperature is 38.3°C. She does not respond verbally to any questions or follow any commands. Her strength is intact in her upper and lower extremities and her reflexes are normal. Examination of her cerebrospinal fluid demonstrates a white blood cell count of 15 cells/μL, a red blood cell count of 500 cells/μL, glucose of 60, and protein of 100. While awaiting further tests, what treatment could you initiate?

A. Ceftriaxone IV and vancomycin IV
B. Ampicillin IV
C. Acyclovir IV
D. Ganciclovir IV
E. None

III-55. Ms. Magz is a 33-year-old high school physics teacher who presents to the emergency department with 1 day of fever, severe headache, and neck pain. She has no past medical history and has had no head trauma. Her only medication is an oral contraceptive. On examination, she is acutely unwell. Her temperature is 40°C, heart rate is 122 beats/min, and blood pressure is 105/65. She has a markedly stiff neck that resists passive movement. She communicates normally, has normal strength in her upper and lower extremities, and has normal reflexes and sensation. There is no skin rash. You draw blood cultures. What should your next step be?

A. Perform lumbar puncture
B. Order CT of the head
C. Initiate vancomycin and ceftriaxone
D. Initiate vancomycin, ceftriaxone, acyclovir, and dexamethasone
E. Initiate vancomycin, ceftriaxone, ampicillin, and dexamethasone

III-56. All of the following are predisposing conditions that increase the risk for development of acute bacterial meningitis due to *Streptococcus pneumoniae* EXCEPT:

A. Alcoholism
B. Pneumococcal pneumonia
C. Pneumococcal sinusitis
D. Pregnancy
E. Splenectomy

III-57. A 28-year-old female is admitted to the intensive care unit with fever, headache, and somnolence. She required intubation for airway protection and was initiated on empiric antibiotics for meningitis. The medical team is unable to successfully perform a lumbar puncture until her second hospital day. Gram stain of her cerebrospinal fluid shows gram-negative diplococci. All of the following individuals should receive chemoprophylaxis with either rifampin, azithromycin, or ceftriaxone EXCEPT:

A. Her 8-year-old son who lives with her.
B. Her sister who she saw the day she became ill.
C. The emergency department physician who performed her intubation while wearing a mask but not eye protection.
D. The taxi driver who drove her the 5 minutes to the hospital.
E. All of the above should receive prophylaxis.

III-58. A 65-year-old man with a past medical history of hypertension presents with a constant, dull, aching generalized headache for the past 10 days with subjective fevers.

For the last day, he has had difficulty speaking. Per his wife, prior to this he had noticed difficulty hearing with his left ear and pain and tenderness in his left inner ear with white cheese-like drainage. On examination, his temperature is 37.9°C, heart rate 105 beats/min, and blood pressure 142/80. Sinuses are nontender. Left ear tympanic membrane has perforated and there is purulent drainage. In addition, his left mastoid is tender. He has aphasia and an upper homonymous quadrantanopia. A CT shows a 4-cm focal area of hypodensity surrounded by ring enhancement with surrounding edema in the left temporal lobe. Which of the following is the appropriate next step?

A. IV vancomycin, cefepime, and dexamethasone
B. Lumbar puncture for cell count, glucose, protein, Gram stain, and culture
C. MRI of the brain
D. Neurosurgery consult for drainage

III-59. All of the following are appropriate empiric antibiotic therapy for infections caused by a bite in a patient with no drug allergies EXCEPT:

A. Dog: ciprofloxacin
B. Cat: amoxicillin-clavulanate
C. Rat: penicillin
D. Human: ampicillin-sulbactam

III-60. The use of an alcohol-based hand rub would be inadequate after leaving the room of which of the following patients?

A. A 20-year-old renal transplant recipient with varicella pneumonia
B. A 40-year-old man with methicillin-resistant *Staphylococcus aureus* furunculosis
C. A 35-year-old woman with advanced HIV and cavitary pulmonary tuberculosis
D. A 54-year-old quadriplegic man admitted with a urinary tract infection due to extended-spectrum β-lactamase–producing bacteria
E. A 78-year-old nursing home resident with recent antibiotic use and *Clostridium difficile* infection

III-61. During the first 2 weeks following solid organ transplantation, which type of infection is most common?

A. Cytomegalovirus and Epstein-Barr virus reactivation
B. HIV-associated infections (e.g., meningococcemia, invasive *Streptococcus pneumoniae* infection)
C. Neutropenia-associated infection (e.g., aspergillosis, candidemia)
D. T-cell deficiency–associated infections (e.g., *Pneumocystis jiroveci*, nocardiosis, cryptococcosis)
E. Typical hospital-acquired infections (e.g., central line infection, hospital-acquired pneumonia, urinary tract infection)

III-62. A 52-year-old man underwent a deceased donor renal transplant 3 months ago for end-stage renal disease due to diabetic nephropathy. He presents today with fever and diarrhea. His white blood cell count is 1500/μL, and his creatinine has increased from 0.6 to 1.9 mg/dL. Which of the following interventions is the most likely to have prevented this acute illness?

A. Isoniazid
B. IVIg
C. Trimethoprim-sulfamethoxazole
D. Valacyclovir
E. Valganciclovir

III-63. Which of the following pathogens are cardiac transplant patients at unique risk for acquiring from the donor heart early after transplant compared with other solid organ transplant patients?

A. *Cryptococcus neoformans*
B. Cytomegalovirus
C. *Pneumocystis jiroveci*
D. *Staphylococcus aureus*
E. *Toxoplasma gondii*

III-64 to III-68. Match each antibiotic with its mechanism of action

III-64. Penicillin

III-65. Clarithromycin

III-66. Levofloxacin

III-67. Gentamicin

III-68. Trimethoprim-sulfamethoxazole

A. Binds to 30S ribosomal subunit of bacteria to inhibit protein synthesis
B. Binds to 50S ribosomal subunit of bacteria to inhibit protein synthesis
C. Inhibits cell wall synthesis by binding to transpeptidase enzymes involved in peptide cross-linking
D. Inhibits DNA gyrase and topoisomerase to inhibit DNA synthesis
E. Inhibits two steps of folate synthesis to disrupt bacterial nucleic acid synthesis

III-69. A 22-year-old man with cystic fibrosis was admitted to the hospital for an exacerbation of his underlying disease. He is known to be colonized with *Pseudomonas aeruginosa*. His usual empiric antibiotic regimen is ceftazidime 2 g IV every 8 hours and tobramycin 10 mg/kg once daily. Which statement best describes the pharmacokinetics and pharmacodynamics of this combination of agents in the treatment of a patient with cystic fibrosis?

A. Aminoglycoside antibiotics such as tobramycin kill bacteria in a time-dependent fashion and thus need higher concentrations of antibiotics.
B. Assessing trough levels of aminoglycosides will help determine whether the appropriate drug level to achieve optimal killing of organisms has occurred.
C. For β-lactam antibiotics, the duration of time with a concentration of drug above the minimal inhibitory concentration determines the killing effect.
D. Lower doses of antibiotics are typically required because cystic fibrosis patients have a higher volume of distribution of antibiotics.
E. Steady-state concentration of the drugs will be reached in three to four half-lives of the drug.

III-70. A woman is 24-weeks pregnant with her first child. She develops a cellulitis in the right leg and requires antibiotic treatment. Which of the following antibiotics should **not** be used during the second and third trimesters of pregnancy?

A. Amoxicillin
B. Azithromycin
C. Clindamycin
D. Doxycycline
E. Vancomycin

III-71. A 73-year-old woman has recurrent urinary tract infections. She is placed on suppressive antibiotic therapy by her primary physician. One year later, she is complaining of progressive dyspnea, and a chest radiograph shows development of pulmonary fibrosis. Which antibiotic could explain development of this complication?

A. Cefaclor
B. Cephalexin
C. Ciprofloxacin
D. Nitrofurantoin
E. Trimethoprim-sulfamethoxazole

III-72. A 48-year-old woman has been hospitalized for 30 days following a stabbing with penetrating chest and abdominal trauma. She had a right-sided hemopneumothorax as well as large bowel injury requiring hemicolectomy and hepatic contusion. She presented in hemodynamic shock and subsequently developed multiorgan failure due to septic shock. She remains critically ill on mechanical ventilation via a tracheostomy tube and on hemodialysis. She had been off vasopressors for 1 week but became acutely febrile overnight with a drop in her blood pressure to 72/38 and heart rate of 148 beats/min. The patient has new infiltrates on chest radiograph and increased thick yellow secretions from her tracheostomy tube. Recently, the surgical intensive care unit has had multiple cases of *Escherichia coli* that produce an extended-spectrum β-lactamase (ESBL). Which of the following statements regarding the ESBL bacteria is true?

A. An ESBL-producing organism is unlikely to be the cause of the patient's recurrent sepsis because bacteria that produce ESBL rarely cause ventilator-associated pneumonia.
B. An ESBL-producing organism is unlikely to cause the patient's recurrent sepsis because the resistance mechanism does not promote easy transmission of organisms among patients within the intensive care unit.
C. The resistance mechanism in ESBL-producing bacteria is related to a genetic mutation that passes down generations.
D. The resistance mechanism in ESBL-producing organisms is plasmid-mediated and is easily passed among bacteria.

III-73. In the patient described above, which of the following empiric antibiotics would have the most likely efficacy against a presumed ESBL infection?

A. Aztreonam
B. Cefazolin
C. Cefepime
D. Meropenem
E. Nafcillin

III-74. All of the following statements regarding pneumococcus (*Streptococcus pneumoniae*) are true EXCEPT:

A. Asymptomatic colonization does not occur.
B. Infants (<2 years old) and the elderly are at greatest risk of invasive disease.
C. Pneumococcal vaccination has impacted the epidemiology of disease.
D. The likelihood of death within 24 hours of hospitalization for patients with invasive pneumococcal pneumonia has not changed since the introduction of antibiotics.
E. There is a clear association between prior viral upper respiratory infection and secondary pneumococcal pneumonia.

III-75. You are examining a blood culture from a recently admitted 75-year-old man with fever. You note that the bacteria growing on the blood agar plate have produced a greenish color and seem to be inhibited by an optochin disc (Figure III-75). They appear shiny. On microscopic examination, you note chains of spherical gram-positive organisms. On direct testing, you note a positive quellung reaction. What bacteria are causing the patient's fever?

A. *Pseudomonas aeruginosa*
B. *Staphylococcus aureus*
C. Coagulase-negative staphylococci
D. *Streptococcus pneumoniae*
E. *Streptococcus pyogenes*

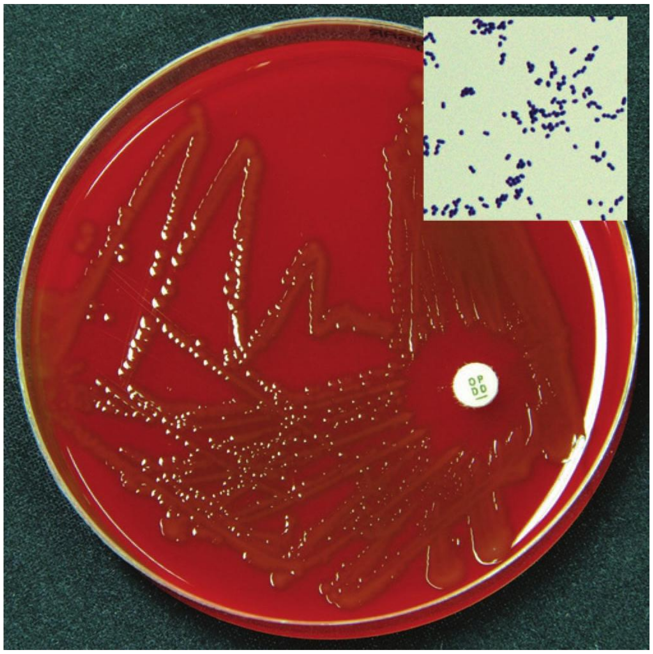


FIGURE III-75 Used with permission from Paul Turner, University of Oxford, United Kingdom.

III-76. Which of the following statements regarding pneumococcal (*Streptococcus pneumoniae*) pneumonia is true?

A. Blood cultures are positive in a majority of cases.
B. In adults, pneumococcal urinary antigen testing has a positive predictive value.
C. On imaging, typically only one lobe is involved.
D. Pulmonary abscess is the most common local complication of pneumococcal pneumonia.
E. The etiologic diagnosis for pneumococcal pneumonia can be made with sputum culture and Gram staining.

III-77. Which of the following statements regarding infections due to pneumococcus (*Streptococcus pneumoniae*) is true?

A. An appropriate therapy for an adult believed to have pneumococcal meningitis is vancomycin in combination with ceftriaxone.
B. Azithromycin provides as much treatment efficacy for pneumococcal infections as amoxicillin.
C. Fluoroquinolone resistance has yet to be observed for pneumococcus.
D. For outpatient management of noninvasive pneumococcal infections, fluoroquinolones provide an efficacy advantage over amoxicillin.
E. Penicillin resistance has yet to be observed for pneumococcus.

III-78. You are taking care of a 56-year-old man with a history of hypertension. Five days prior, he developed the acute onset of fever, chills, and myalgias. He had a rapid molecular assay for influenza via a nasopharyngeal swab 2 days prior, and was diagnosed with influenza and initiated on oseltamivir. His fevers improved and he started to feel better, but this morning he developed fever and rigors again, with shortness of breath and purulent sputum production. You collect an expectorated sputum sample and perform a Gram stain, visualizing the bacteria shown in Figure III-78 under the microscope. The organisms are reported as catalase positive and produce coagulase. Which of the following organisms is likely responsible for this patient's infection?

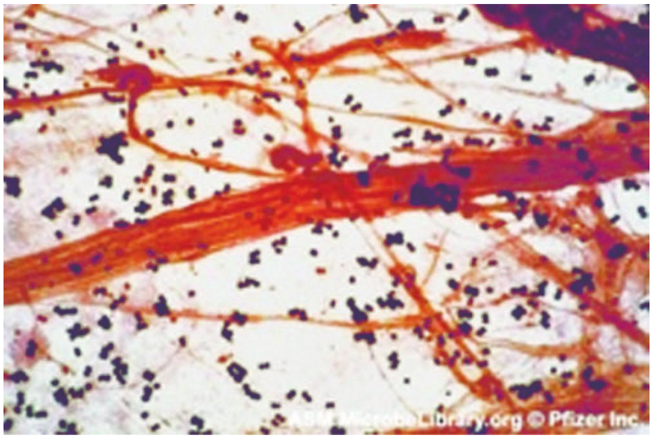


FIGURE III-78 Reproduced with permission from ASM MicrobeLibrary.org. © Pfizer, Inc.

A. *Haemophilus influenzae*
B. *Pseudomonas aeruginosa*
C. *Staphylococcus aureus*
D. *Staphylococcus epidermidis*
E. *Streptococcus pneumoniae*

III-79. Which of the following statements regarding *Staphylococcus aureus* is true?

A. Infections due to *S. aureus* among colonized individuals are almost always due to a strain distinct from their colonizing strain.
B. *S. aureus* is always a pathogen when detected in any human culture.
C. The anterior nares and oropharynx are the most common sites of colonization with *S. aureus*.
D. The majority of people in the United States are colonized with *S. aureus*.

III-80. Ms. Jung is an 18-year-old previously healthy woman who presents with fever and hypotension. On the morning of admission, she felt quite ill with fevers, rigors, nausea, vomiting, and diarrhea. As the day progressed, she developed redness of her skin all over and became lethargic and ultimately quite difficult to arouse. She has no notable past medical history and takes no medications. She does not use alcohol or illicit drugs and is not sexually active. Her parents brought her to the emergency department in the late afternoon where her blood pressure was noted to be 70/50, with a heart rate of 140 beats/min, temperature of 39.5°C, and respiratory rate of 24 breaths/min. Oxygen saturation is 94% on room air. She is minimally responsive. Skin examination reveals generalized erythroderma but no signs of skin tears or infection. Genitourinary examination reveals a retained tampon that is immediately removed. Blood Gram stain and culture are negative at 12 hours. You suspect staphylococcal toxic shock syndrome (TSS). Which of the following statements regarding staphylococcal TSS is true?

A. A skin site infection is clinically apparent in most cases.
B. Blood cultures will likely return positive by 24–36 hours given her grave clinical presentation.
C. Desquamation of the skin will occur within 1–2 days.
D. High-dose IV penicillin should be started immediately.
E. It is caused by a toxin that binds to the invariant region of the major histocompatibility complex and directly stimulates T-cell replication.

III-81. A 28-year-old male with a past medical history of injection drug use presents with 3 days of fever, chills, shortness of breath, and cough productive of yellow sputum, and lower back pain. On initial examination, his temperature is 39.6°C, pulse is 130 beats/min, blood pressure is 95/60, respiratory rate is 40 breaths/min, and oxygen saturation is 94%. On examination, he is disheveled, with arms covered in track marks. He has a II/VI systolic murmur at the left lower sternal border. He has tenderness to palpation on his L2-L3. He has crackles on the right lower lobe of the lung. Blood cultures are positive for gram-positive cocci in clusters. A CT is performed and shown in Figure III-81. He also complains of severe lower back pain. All of the following are appropriate management steps at this time EXCEPT:

A. Initiation of vancomycin
B. Surgical drainage of pulmonary lesion
C. Transthoracic echocardiogram
D. MRI of L-spine

III-82. Which of the following organisms is most likely to cause infection of a shunt implanted for the treatment of hydrocephalus?

A. *Bacteroides fragilis*
B. Coagulase-negative *Staphylococcus*
C. *Corynebacterium diphtheriae*
D. *Escherichia coli*
E. *Staphylococcus aureus*

III-83. Which of the following populations are at risk for colonization with *Staphylococcus aureus*?

A. Insulin-dependent diabetics
B. Patients receiving hemodialysis
C. Injection drug users
D. Individuals with skin damage
E. All of the above

III-84. A 60-year-old woman with a past medical history of well-controlled diabetes presents with the rapid onset of fever, chills, and a painful, warm, and shiny bright red lesion on the malar area of her face over the last 6 hours. On examination, she has a temperature of 38.3°C, blood pressure of 125/83, and heart rate of 102 beats/min. Her examination is significant for a rash on her face (Figure III-84). She has

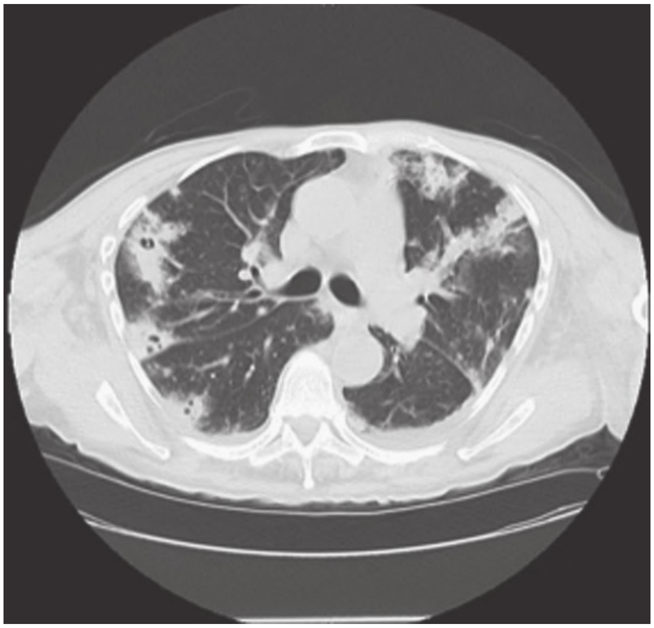


FIGURE III-81

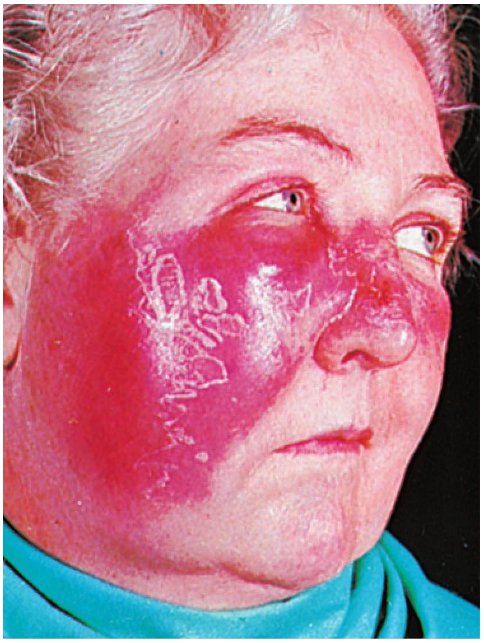


FIGURE III-84

no antibiotic allergies. Which of the below is the first line treatment for her condition?

A. Doxycycline
B. Penicillin G
C. Levofloxacin
D. Linezolid
E. Trimethoprim-sulfamethoxazole

III-85. A 36-year-old man is brought to the hospital by his wife because of a rapidly worsening skin infection. The patient has a history of type 1 diabetes, and his last documented hemoglobin A1c was 5.5%. His wife reports that he had a small insect bite on his calf a few days ago with some redness. Over the course of today, he has developed severe thigh pain initially with no redness, but over the last 1 hour, there has been worsening pain and swelling with some mottling of the skin. He also reports that he feels like his thigh and calf are numb. He is febrile and tachycardic. Physical examination reveals marked tenderness and tenseness of the right leg from the thigh down. There is some redness and mottling. A femoral and posterior tibial pulse are present. CT scan of the leg shows extensive inflammation of the fascial planes but no evidence of muscle inflammation. Which of the following organisms is most likely responsible for his infection?

A. *Clostridium difficile*
B. *Staphylococcus aureus*
C. *Staphylococcus epidermidis*
D. *Streptococcus pneumoniae*
E. *Streptococcus pyogenes*

III-86. You are seeing a 17-year-old adolescent with no notable past medical history or medication allergies. He states that for the past 3 days he has noticed an increasingly sore throat, cough, runny nose, and painful "knots" on his neck. On examination, he is afebrile, has pharyngeal erythema, tonsillar exudate, and bilateral posterior tender cervical adenopathy (nodes <1.5 cm). A rapid latex agglutination test for group A streptococci is negative. Which of the following statements is true in this patient?

A. Azithromycin orally should be initiated given the clinical suspicion for streptococcal pharyngitis.
B. If antibiotic therapy is initiated, a 5-day duration is generally sufficient.
C. Pharyngeal swab for culture should be performed.
D. The clinical scenario is classic for streptococcal pharyngitis.
E. The negative rapid test effectively rules out streptococcal pharyngitis.

III-87. A 32-year-old woman with no medication allergies presents in active labor at 36 weeks' gestation. While her labor is progressing normally, you review her chart and note that a genitourinary culture for group B streptococci was not performed during this pregnancy, despite the fact that the patient had a previous child with infectious complications due to group B *Streptococcus*. Which of the following is the most appropriate course of action for this delivery?

A. Immediately perform a swab and rapid nucleic acid amplification test for group B *Streptococcus* to determine the need for treatment.
B. Initiate therapy with penicillin G.
C. Perform a perineal swab and gram stain. The presence of any gram-positive cocci should prompt antibiotic prophylaxis.
D. Provided that the patient does not have prolonged rupture of membranes or fever, no testing or treatment is required.

III-88. Which of the following statements regarding the epidemiology of enterococcal infections is true?

A. Enterococcal infections are rare as a cause of nosocomial infections.
B. Human colonization with enterococci is rare.
C. Resistance to vancomycin among *Enterococcus faecium* isolates remains rare.
D. The majority of *Enterococcus faecalis* isolates are sensitive to β-lactams, particularly ampicillin.
E. The risk of mortality is equivalent among patients infected with vancomycin-resistant and vancomycin-susceptible strains of *Enterococcus*.

III-89. Which of the following statements regarding enterococcal infections is true?

A. Enterococci are a common cause of meningitis.
B. Enterococci are a common cause of central line–associated bloodstream infections.
C. Most enterococcal urinary tract infections occur in patients who have normal urinary tracts.
D. Poor dentition and gingival disease are the usual proximal sources for enterococcal bacteremia.
E. Presence of enterococci in a sterilely obtained urine culture usually warrants treatment.

III-90. A 74-year-old man with a recent history of diverticulitis is admitted to the hospital with 1 week of fever, malaise, and generalized weakness. His physical examination is notable for a temperature of 38.5°C, a new mitral heart murmur, and splinter hemorrhages. Three blood cultures grow *Enterococcus faecalis*, and an echocardiogram shows a small vegetation on the mitral valve. The organism is reported as being sensitive to ampicillin. Based on this information, which of the following is recommended therapy?

A. Ampicillin
B. Ampicillin plus ceftriaxone
C. Daptomycin
D. Linezolid
E. Tigecycline

III-91. Which of the following statements regarding *Corynebacterium diphtheriae* infections is true?

A. Alcoholism is a risk factor for adult diphtheria infections.
B. Birds and horses provide animal reservoirs for *C. diphtheriae*.
C. Childhood vaccination imparts lifelong protective immunity to patients who receive the proper vaccination course.
D. Cutaneous diphtheria is almost always caused by a toxigenic strain.
E. Development of an effective vaccination has eliminated adult diphtheria infections in the United States.

III-92. You are evaluating a 47-year-old woman in the emergency department with fever and sore throat. She is a recent immigrant from Central America and has not yet established primary care. She has been working at a friend's house caring for young children. On examination, she has extensive submandibular and cervical swelling, foul breath, and a tenacious well-demarcated white/gray exudative substance adherent to her oropharynx (Figure III-92). Attempts to remove this pseudomembranous substance result in bleeding. A rapid strep test is negative. The patient is at risk for which of the following complications of this disease?

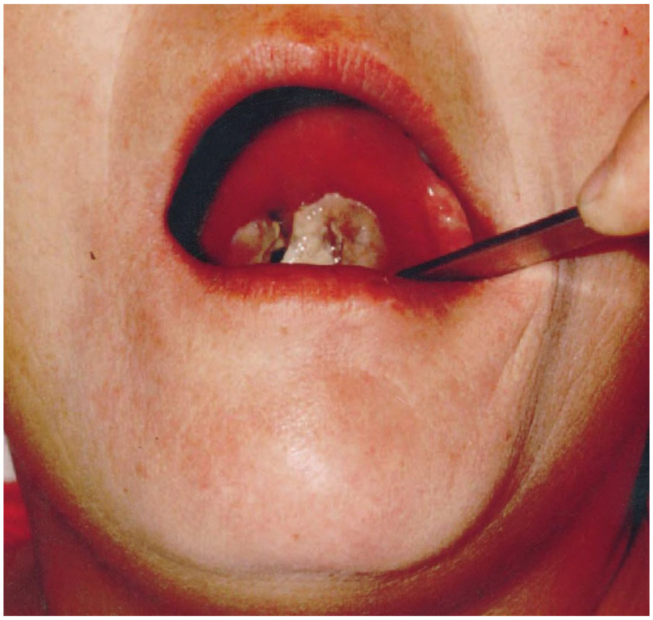


FIGURE III-92 Reproduced with permission from Kadirova R et al: Clinical characteristics and management of 676 hospitalized diphtheria cases, Kyrgyz Republic, 1995. *J Infect Dis* 181:S110, 2000.

A. Epidural abscess
B. Hepatitis
C. Meningitis
D. Myocarditis
E. Rheumatic fever

III-93. You are caring for a 34-year-old pregnant woman with fever, backache, myalgias, headache, and bacteremia. Blood cultures show *Listeria monocytogenes*, and she is promptly initiated on appropriate antibiotic therapy. Of the following, which is the most likely cause of her infection?

A. Droplets from infected co-worker
B. Fecal-oral route
C. Ingestion of deli meat
D. Sexually transmitted
E. Waterborne

III-94. A 50-year-old woman with diabetes mellitus and chronic kidney disease is admitted to the hospital for 7 days of diarrhea and 5 days of altered mental status and headaches. She denies photophobia but does have mild neck stiffness. Cerebrospinal fluid analysis shows a white blood cell count of 800/μL (75% polymorphonuclear leukocytes) with a low-normal glucose level. Which of the following antibiotics is the most appropriate choice for this patient?

A. Ampicillin
B. Azithromycin
C. Cefazolin
D. Ciprofloxacin
E. Moxifloxacin

III-95. A 26-year-old woman presents late in the third trimester of her pregnancy with high fevers, myalgias, backache, and malaise. She is admitted and started on empirical broad-spectrum antibiotics. Blood cultures return positive for *Listeria monocytogenes*. She delivers a 5-lb infant 24 hours after admission. Which of the following statements regarding antibiotic treatment for this infection is true?

A. Clindamycin should be used in patients with penicillin allergy.
B. Neonates should receive weight-based ampicillin and gentamicin.
C. Penicillin plus gentamicin is first-line therapy for the mother.
D. Quinolones should be used for *Listeria* bacteremia in late-stage pregnancy.
E. Trimethoprim-sulfamethoxazole has no efficacy against *Listeria*.

III-96. A 4-day-old female infant is brought emergently to the hospital after her parents noticed behavioral changes and shallow breathing. The infant was born by normal vaginal delivery after an uncomplicated full-term delivery and received normal antenatal care for 48 hours in the hospital. Hospital notes indicate that she had a normal suck and cry as an inpatient. On examination, you note a generalized hypertonia and rigidity throughout the infant's body and occasional spasms. You note a foul-smelling brown material on and around the umbilical stump. Which of the following is true regarding the etiologic agent responsible for this infant's severe illness?

A. At the time of initial clinical presentation, death is most commonly due to cardiovascular complications with this disease.
B. Blood cultures will yield gram-positive rods.
C. Diagnosis of this illness requires laboratory confirmation of the causative organism.
D. The toxin responsible for this illness is active at the peripheral neuromuscular junctions.
E. The toxin responsible for this illness works by inhibiting inhibitory presynaptic neurons, leading to upregulated activity in the motor nervous system.

III-97. A 64-year-old man with a long history of heroin abuse is brought to the hospital because of fever and worsening muscle spasms and pain over the last day. Because of long-standing venous sclerosis, he no longer injects intravenously but "skin-pops," often with dirty needles. On examination, he is extremely sweaty and febrile to 38.5°C (101.4°F). There are widespread muscle spasms, including the face. He is unable to open his jaw due to muscle spasm and has severe back pain due to diffuse spasm. On his leg, there is a skin wound that is tender and erythematous. All of the following statements regarding this patient are true EXCEPT:

A. Culture of the wound may reveal *Clostridium tetani*.
B. Intrathecal antitoxin administration is recommended therapy.
C. Metronidazole is recommended therapy.
D. Permanent muscle dysfunction is likely after recovery.
E. Strychnine poisoning and antidopaminergic drug toxicity should be ruled out.

III-98. A 24-year-old woman with a history of developmental delay who lives in a group home is brought to the hospital for weakness starting in the head and descending to her legs. She has symmetric cranial nerve palsies, inability to move, and decreased breathing. Deep tendon reflexes are normal. On examination, she is taking only shallow respirations, and you note flaccid muscle tone throughout. There was no preceding fever, cough, coryza, rash, or new medications. She was recently given amoxicillin-clavulanate for sinusitis. She had been eating many foods created with prepared meats. Which of the following is the most likely cause of her presentation?

A. Botulinum toxicity
B. Guillain-Barré syndrome
C. Hypokalemic periodic paralysis
D. Tetanus toxicity
E. Tick paralysis

III-99. You are completing a clinical rotation in Papua New Guinea. Today, two adults present only hours apart to the emergency department with remarkably similar cases. Both had attended a pig feast yesterday and awoke today with excruciating abdominal pain. Both CT scans show extensive necrosis of the intestinal wall, most severely in the jejunum. The causative organism of these infections is also most commonly causative in cases of which of the following?

A. Cellulitis
B. Gas gangrene myonecrosis
C. Meningitis
D. Pharyngitis
E. Pneumonia

III-100. A 19-year-old man presents to the emergency department with 4 days of watery diarrhea, nausea, vomiting, and low-grade fever. He recalls no unusual meals, sick contacts, or travel. He is hydrated with IV fluid, given antiemetics, and discharged home after feeling much better. Three days later, two of three blood cultures are positive for *Clostridium perfringens*. He is called at home and says that he feels fine and is back to work. What should your next instruction to the patient be?

A. Reassurance
B. Return for IV penicillin therapy
C. Return for IV penicillin therapy plus echocardiogram
D. Return for IV penicillin therapy plus colonoscopy
E. Return for surveillance blood culture

III-101. During your freshman year of college, you perform an experiment for your microbiology class. You obtain nasopharyngeal swab cultures on your roommates to analyze the colonizing bacteria there. You find that one of your roommates has evidence of *Neisseria meningitidis* from his culture. When he returns from class, he says he has been feeling fine. He does not think he has been vaccinated against meningococcus. What treatment, if any, should this student receive?

A. Ceftriaxone 1 g IM
B. Mupirocin cream to the bilateral nares twice daily
C. Admit to the hospital for IV ceftriaxone 2 g daily for 14 days
D. No action

III-102. A 21-year-old college student is admitted to the hospital with meningitis. Cerebrospinal fluid cultures reveal *Neisseria meningitides* type B. The patient lives in a dormitory suite with five other students. Which of the following is recommended for the close household contacts?

A. Culture all close contacts and offer prophylaxis to those with positive cultures
B. Immediate administration of ceftriaxone to all close contacts
C. Immediate administration of rifampin to all close contacts
D. Immediate vaccination with conjugate vaccine
E. No therapy necessary

III-103. All of the following individuals should receive the routine meningococcal conjugate vaccination EXCEPT:

A. All adults over the age of 60
B. All preteens and teens between the ages of 11 and 16
C. Patients with a complement deficiency
D. Patients with asplenia
E. Microbiologists who are routinely exposed to *Neisseria meningitides*

III-104. You are seeing a 23-year-old woman who is 3 months pregnant and is sexually active. She has been experiencing dysuria and vaginal discharge. Gram stain of her vaginal discharge is shown in Figure III-104. She has no known medication allergies. Which of the following is the most reasonable medical regimen for the treatment of her infection?

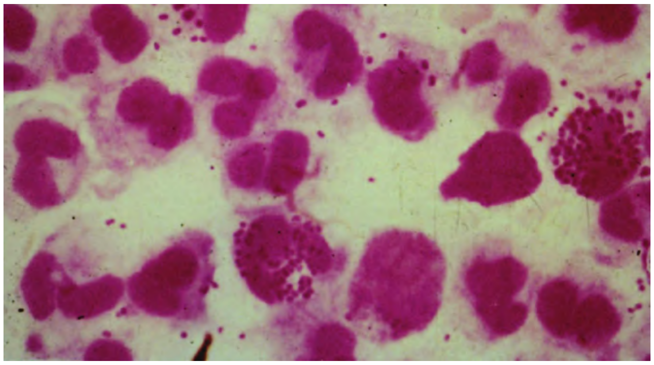


FIGURE III-104 ©All rights reserved. Gram stain of urethral discharge. Boehringer-Ingelheim, 2002. Reproduced with permission from the Minister of Health, 2015.

A. Ceftriaxone 250 mg IM once
B. Ceftriaxone 250 mg IM and azithromycin 1 g orally once
C. Ceftriaxone 250 mg IM once and doxycycline 100 mg orally twice daily for 7 days
D. Ciprofloxacin 500 mg twice daily for 10 days
E. Cefixime 400 mg orally once and azithromycin 1 g orally once

III-105. A 27-year-old man presents to the hospital with fever, chills, and migratory polyarthralgias. You note skin lesions including papules, pustules, and bullae with a hemorrhagic component on the extremities (Figure III-105). Some of the skin lesions appear necrotic. Aspiration of a painful knee reveals gram-negative diplococci, and you make the diagnosis of disseminated gonococcal infection/arthritis (DGI). Oddly, this is his second bout of DGI in the past 2 years. Which of the following disease should be particularly screened for in this patient?

A. Chédiak-Higashi syndrome
B. Common variable immunodeficiency
C. Leukemia
D. Neutropenia
E. Total hemolytic complement activity

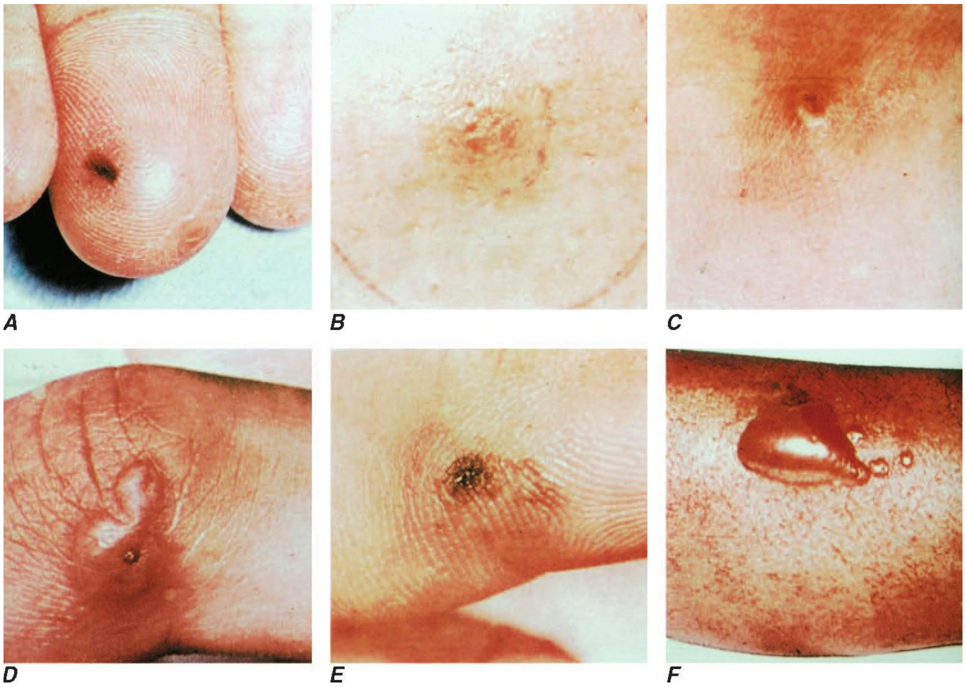


FIGURE III-105 Reproduced with permission from Holmes KK: Disseminated gonococcal infection. *Ann Intern Med*. 74:979, 1971.

III-106. All of the following statements regarding *Moraxella catarrhalis* are true EXCEPT:

A. First-line treatment for *M. catarrhalis* is amoxicillin-clavulanate.
B. It causes 20% of episodes of acute bacterial sinusitis in children.
C. It is a factor in as much as 10% of chronic obstructive pulmonary disease exacerbations.
D. It is one of the three most common causes of childhood otitis media.
E. Nasopharyngeal colonization increases with age.

III-107. A 44-year-old man presents to the emergency department for evaluation of a severe sore throat. His symptoms began this morning with mild irritation on swallowing and have gotten progressively severe over the course of 12 hours. He has been experiencing a fever to as high as 39°C at home and also reports progressive shortness of breath. He denies antecedent rhinorrhea or tooth or jaw pain. He has had no ill contacts. On physical examination, the patient appears flushed and in respiratory distress with use of accessory muscles of respiration. Inspiratory stridor is present. He is sitting leaning forward and is drooling with his neck extended. His vital signs are as follows: temperature 39.5°C, blood pressure 116/60, heart rate 118 beats/min, respiratory rate 24 breaths/min, and SaO_2 95% on room air. Examination of his oropharynx shows erythema of the posterior oropharynx without exudates or tonsillar enlargement. The uvula is midline. There is no sinus tenderness and no cervical lymphadenopathy. His lung fields are clear to auscultation, and cardiovascular examination reveals a regular tachycardia with a II/VI systolic ejection murmur heard at the upper right sternal border. Abdominal, extremity, and neurologic examinations are normal. Laboratory studies reveal a white blood cell count of 17,000/μL with a differential of 87% neutrophils, 8% band forms, 4% lymphocytes, and 1% monocytes. Hemoglobin is 13.4 g/dL, with a hematocrit of 44.2%. An arterial blood gas on room air has a pH of 7.32, a PCO_2 of 48 mmHg, and a PO_2 of 92 mmHg. A lateral neck film shows an edematous epiglottis. What is the next most appropriate step in evaluation and treatment of this individual?

A. Ampicillin 500 mg IV every 6 hours
B. Ceftriaxone 1 g IV every 24 hours
C. Endotracheal intubation and ampicillin 500 mg IV every 6 hours
D. Endotracheal intubation, ceftriaxone 1 g IV every 24 hours, and clindamycin 600 mg IV every 6 hours
E. Laryngoscopy and close observation

III-108. All of the following statements regarding the HACEK organisms are true EXCEPT:

A. HACEK bacteremia is very predictive of underlying infective endocarditis.
B. HACEK organisms normally reside on the skin.
C. It typically takes over a week for HACEK organisms to grow in the microbiology lab.
D. They are typically cultured on media routinely used for enteric bacteria.
E. Their growth requires an atmosphere of carbon dioxide.

III-109. A 38-year-old woman with frequent hospital admissions related to alcoholism comes to the emergency department after being bitten by a dog. There are open wounds on her arms and right hand that are purulent and have necrotic borders. She is hypotensive and is admitted to the intensive care unit. She is found to have disseminated intravascular coagulation and soon develops multiorgan failure. Which of the following is the most likely organism to have caused her rapid decline?

A. *Aeromonas* spp.
B. *Capnocytophaga* spp.
C. *Eikenella* spp.
D. *Haemophilus* spp.
E. *Staphylococcus* spp.

III-110. *Legionella* outbreaks are usually tied to which of the following?

A. A significant population of unvaccinated individuals
B. Bioterrorism attacks
C. Contaminated aquatic reservoir
D. Equine animal reservoir and zoonotic transmission
E. Surgical wound infections

III-111. All of the following statements regarding *Legionella* pneumonia (Legionnaires disease) are true, EXCEPT:

A. Ataxia and speech difficulties are the most severe extrapulmonary sequela of Legionnaires disease.
B. Gastrointestinal complaints are more common in Legionnaires disease than other types of bacterial pneumonia.
C. Hyponatremia is common in patients with Legionnaires disease.
D. Most patients with Legionnaires disease have fever.
E. The prognosis of Legionnaires disease is similar to that of other “atypical” pneumonias.

III-112. A 56-year-old man with a history of hypertension and cigarette smoking is admitted to the intensive care unit after 1 week of fever and nonproductive cough. Imaging shows a new pulmonary infiltrate, and urine antigen test for *Legionella* is positive. Each of the following is likely to be an effective antibiotic EXCEPT:

A. Azithromycin
B. Aztreonam
C. Levofloxacin
D. Doxycycline
E. Trimethoprim-sulfamethoxazole

III-113. A 69-year-old woman who lives at home is admitted to the intensive care unit with respiratory failure. She has fever to 39°C, obtundation, and bilateral parenchymal consolidation on chest imaging. Her family notes 3–4 days of abdominal pain, nausea, and vomiting prompting strong consideration of Legionella pneumonia. Which of the following tests has the highest sensitivity for *Legionella*?

A. Antibody testing
B. Culture of sputum
C. Culture of transtracheal aspirate
D. Direct fluorescent staining of sputum
E. Urinary antigen testing

III-114. Which of the following statements regarding pertussis infection is true?

A. Cyclical outbreaks of pertussis occur every 17 years.
B. In unimmunized populations, pertussis incidence peaks in infancy.
C. Internationally, two in three cases of pertussis occur in developing nations.
D. Pertussis has an attack rate of at least 80% among unimmunized household contacts.
E. School-aged children are the major source of pertussis infection to high-risk infants.

III-115. An 18-year-old man seeks attention for a severe cough. He reports no past medical history and excellent health. Approximately 7 days ago, he developed an upper respiratory syndrome with low-grade fever, coryza, some cough, and malaise. The fever and coryza have improved over the last 2 days, but he has an episodic cough that is often severe enough to result in vomiting. He reports receiving all infant vaccinations, but only influenza vaccinations in the last 12 years. He is afebrile, and while not coughing, his chest examination is normal. During a coughing episode, there is an occasional inspiratory whoop. Chest radiograph is unremarkable. Which of the following is true regarding his likely illness?

A. A fluoroquinolone is recommended therapy.
B. Cold agglutinins may be positive.
C. Nasopharyngeal aspirate for DNA testing is likely to be diagnostic.
D. Pneumonia is a common complication.
E. Urinary antigen testing remains positive for up to 3 months.

III-116. In healthy individuals, which of the following bacteria species is the predominant gram-negative bacillus in the colonic flora?

A. Klebsiella
B. *Proteus*
C. *Escherichia coli*
D. *Staphylococcus*
E. *Clostridium*

III-117. An 82-year-old woman with a history of dementia who resides at a long-term care facility presents to the emergency department with fevers, altered mental status, and discomfort with urination. Of note, the nursing home has a high rate of antibiotic use and has admitted several patients over the last year with extended-spectrum β-lactamase inhibitor (ESBL) infections. On examination, she is thin and acutely ill appearing. She has a temperature of 38.9°C, a blood pressure of 85/55, a heart rate of 95 beats/min, and a respiration rate of 18 breaths/min. Urinalysis shows 200 white blood cells per high-powered field and many bacteria. Blood cultures are growing gram-negative rods. Which of the following is the most appropriate empiric therapy in this patient?

A. Cefepime
B. Meropenem
C. Piperacillin-tazobactam
D. Vancomycin and cefepime
E. Vancomycin and piperacillin-tazobactam

III-118. Ms. Posada is a 32-year-old sexually active woman with no past medical history. She presents to your acute care clinic with a complaint of burning urination for the past 4 days. Yesterday, she noticed that her left flank and her back were also painful, and she began having fevers up to 39°C (102°F). She has three sexual partners and frequently has unprotected vaginal intercourse with them, although she does not consider any of them high risk for sexually transmitted infections. Her examination is notable for a temperature of 39°C, heart rate of 105 beats/min, and blood pressure of 105/65, left costophrenic angle tenderness, and an otherwise benign abdominal/pelvic examination. Clean catch urinalysis shows positive leukocyte esterase, a high white blood cell count, and no epithelial cells. You suspect pyelonephritis. Which of the following organisms is the most common cause of this infection?

A. *Escherichia coli*
B. *Klebsiella oxytoca*
C. *Proteus mirabilis*
D. *Staphylococcus aureus*
E. *Staphylococcus saprophyticus*

III-119. Which of the following statements regarding Shiga toxin–producing and enterohemorrhagic *Escherichia coli* is true?

A. Cattle are the major reservoir for infection.
B. Gross bloody diarrhea with high fever is the most common clinical manifestation.
C. Person-to-person transmission does not occur.
D. Shiga toxin–producing *E. coli* is the most common cause of bacterial diarrhea in the United States.
E. The incubation period is 12–24 hours.

III-120. A 27-year-old woman who is 3 weeks postpartum and is breastfeeding presents with a temperature of 38.5°C and a painful, indurated patch on her right breast. She is very concerned because her breast milk has also turned pink. Which of the following organisms is the most likely cause of her condition?

A. *Staphylococcus aureus*
B. *Candida albicans*
C. *Pseudomonas aeruginosa*
D. *Serratia marcescens*
E. *Escherichia coli*

III-121. A 53-year-old man has been in the intensive care unit for 1 month with complications of acute pancreatitis. He had experienced acute respiratory distress syndrome and remains on mechanical ventilation through a tracheostomy. Over the last week, he has had gradual lessening of his mechanical ventilator needs. However, over the last day, his FiO_2 requirements increased from 0.4 to 0.8 and he has developed a newly purulent sputum and a right lower lobe infiltrate. He has a temperature of 38.3°C. A sputum culture grows *Acinetobacter baumannii*. All of the following statements regarding *Acinetobacter* infections are true EXCEPT:

A. *Acinetobacter* infections are an increasingly common cause of outbreaks in hospitals.
B. *Acinetobacter* is frequently resistant to multiple antibiotics.
C. *Acinetobacter* is a common cause of community-acquired pneumonia.
D. Hospital-acquired pneumonia caused by *Acinetobacter* occurs later than other pathogens.
E. Carbapenem use is the major risk factor for carbapenem-resistant *Acinetobacter*.

III-122. You are taking care of Mrs. Brosius, a 74-year-old woman who was admitted to the intensive care unit 12 days prior with a chronic obstructive pulmonary disease exacerbation. Unfortunately, she has remained dependent on mechanical ventilation and is still sedated and intubated. Today, her nurse noted that her tracheal suction secretions have increased in volume and tenacity, and a chest x-ray confirms a new infiltrate. Laboratory values reveal a rising serum white blood cell count, and her oxygen requirement has increased slightly. Sputum culture confirms *Acinetobacter baumannii*. You know that this is a particularly difficult organism to treat due to which of the following properties?

A. Chronic carrier status in the biliary system of many critically ill patients
B. The ability to acquire or upregulate a wide range of antibiotic resistance determinants
C. The ability to form antibiotic-resistant spores
D. The ability to form biofilms that are nearly impenetrable to most antibiotics
E. Very slow growth requiring long courses (>4 weeks) of antibiotics

III-123. You are conducting a research study to determine whether socioeconomic status is correlated with *Helicobacter pylori* colonization. Today, your subject is a 35-year-old high school teacher. The subject drinks a solution of urea labeled with nonradioactive 13C isotope. He then blows into a tube. Your instruments detect carbon dioxide containing 13C. Which of the following is true regarding this patient?

A. Histologic examination of gastric tissue is unlikely to reveal gastritis in this patient.
B. The results of this test indicate that this patient has a higher risk of gastric adenocarcinoma.
C. The same test performed a year later in the absence of treatment will likely not detect carbon dioxide containing 13C in the patient's exhalation.
D. This patient has a higher risk of colon cancer.
E. This patient is not colonized with *H. pylori*.

III-124. A 36-year-old man with heme occult-positive stools and a history of epigastric pain is found to have *Helicobacter pylori* infection. All of the following are effective eradication regimens EXCEPT:

A. Amoxicillin and levofloxacin for 14 days
B. Omeprazole, amoxicillin, clarithromycin, and tinidazole for 14 days
C. Omeprazole, bismuth subsalicylate, tetracycline, and metronidazole for 14 days
D. Omeprazole, amoxicillin, and levofloxacin for 10 days

III-125. One month after receiving a 14-day course of omeprazole, clarithromycin, and amoxicillin for *Helicobacter pylori*–associated gastric ulcer disease, a 44-year-old woman still has mild dyspepsia and pain after meals. Which of the following is the appropriate next step in her management?

A. Empirical long-term proton pump inhibitor therapy
B. Endoscopy with biopsy to rule out gastric adenocarcinoma
C. *H. pylori* serology testing
D. Second-line therapy for *H. pylori* with omeprazole, bismuth subsalicylate, tetracycline, and metronidazole
E. Urea breath test

III-126. A 62-year-old female with a past medical history of chronic obstructive pulmonary disease presented with community-acquired pneumonia requiring intubation. She is placed on overly broad antibiotic therapy with meropenem and azithromycin and her fevers resolve, but she remains intubated. On the seventh day on the ventilator, she develops a temperature of 38.5°C, an increase in her sputum production, and an increase in the oxygen required to maintain oxygenation from an FiO_2 of 0.40 to an FiO_2 of 0.60. Sputum cultures show *Stenotrophomonas maltophilia*. What should you initiate to treat her condition?

A. Ceftriaxone and azithromycin
B. Meropenem
C. Piperacillin-tazobactam
D. Trimethoprim-sulfamethoxazole
E. Nothing; *Stenotrophomonas* is likely a contaminant

III-127. A 59-year-old male patient in the cardiac intensive care unit after a coronary artery bypass graft remains intubated 6 days after the procedure. He had been improving, but this morning he developed a temperature of 38.4°C, increased thick sputum production, and an increase in his oxygen requirements from an FiO_2 of 0.40 to an FIO_2 of 0.70. Sputum cultures are obtained and grow *Pseudomonas aeruginosa*. Which of the following is the recommended treatment?

A. Cefepime for a 7-day course
B. Gentamicin for a 7-day course
C. Gentamicin for a 14-day course
D. Gentamicin and cefepime for a 14-day course
E. Meropenem for a 14-day course

III-128. A sputum culture done on a patient with cystic fibrosis with a rapid decline in pulmonary function and a poor clinical prognosis shows which of the following organisms?

A. *Burkholderia cepacia*
B. *Pseudomonas aeruginosa*
C. *Staphylococcus aureus*
D. *Staphylococcus epidermidis*
E. *Stenotrophomonas maltophilia*

III-129. You are taking care of a 65-year-old zoo employee who presents with fever and diarrhea. Ultimately, you diagnose her with nontyphoidal salmonellosis. You know that she must have contracted the infection via which of the following routes?

A. Contact with contaminated fomites
B. Oral ingestion of organisms
C. Respiratory secretions
D. Sexually transmitted
E. Any of the above routes

III-130. You are caring for Mr. Munoz, a previously healthy 65-year-old man who was admitted to the hospital yesterday after having fevers for a week at home. He states that he just got off vacation where he traveled through South Asia, visiting India, Malaysia, and Thailand. He denied any risky sexual or gastronomic behaviors during his travels. On admission, his temperature was 39.7°C, heart rate was 68 beats/min, and blood pressure was 110/60. Examination of his skin reveals a faint, salmon-colored, blanching, maculopapular rash located primarily on the trunk and chest, pictured in Figure III-130. He complains of moderate abdominal pain and nausea. While blood culture reveals no organisms; a bone marrow culture grows gram-negative rods. The bacteria produce acid on glucose fermentation, reduce nitrates, and do not produce cytochrome oxidase or ferment lactose. Closer inspection shows that they are motile by means of flagella. Which of the following organisms is Mr. Munoz most likely infected with?

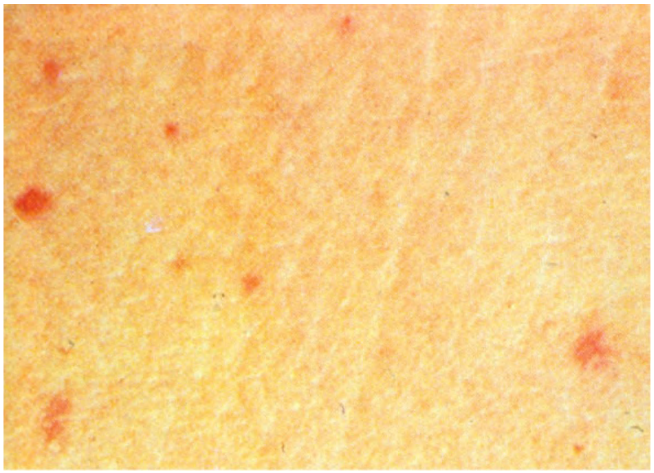


FIGURE III-130

A. *Clostridium difficile*
B. *Entamoeba histolytica*
C. *Escherichia coli*
D. *Klebsiella pneumoniae*
E. *Salmonella typhi*

III-131. A group of four healthy young women all in their 20s, who are roommates and work in the same office, present with crampy abdominal pain, vomiting, copious nonbloody diarrhea, and fever of 38–39°C for 1–2 days. All four present within 24 hours with dehydration. A stool culture from the first one who presented grows *Salmonella enteritidis*. All of the following are likely exposures EXCEPT:

A. Jar of peanut butter
B. Lettuce
C. Shared bathroom
D. Shared pet turtle
E. Undercooked eggs

III-132. A previously healthy 32-year-old woman is visiting Bali, where she swims in a lake and eats street food. She develops crampy abdominal pain, fever to 40°C, nausea, malaise, and bloody diarrhea. Stool cultures grow *Shigella flexneri*. All of the following statements regarding her condition EXCEPT:

A. She does not need antibiotics to treat this infection.
B. She may be at risk for reactive arthritis.
C. The human intestinal track is the major reservoir.
D. Toxic megacolon can be a major complication.
E. Transmission from infected individuals is common.

III-133. A 45-year-old healthy businessman just returned from a trip to Vietnam where he was traveling on vacation. Five days after his return, he developed fever and a headache followed 12 hours later by diarrhea and abdominal pain. The next day, he had >10 bowel movements in 12 hours, the final two with gross blood in the stool, prompting his presentation to the emergency department. His vital signs are as follows: temperature 37.8°C, heart rate 90 beats/min, respiratory rate 14 breaths/min, and oxygen saturation 98% on room air. Gram stain of a stool specimen identifies a small, curved helical-shaped gram-negative rod. You suspect a *Campylobacter* spp. Which of the following statements regarding his most likely infection is true?

A. A single dose of azithromycin is effective therapy.
B. Antibiotics are not helpful. He should receive supportive fluid and electrolyte repletion.
C. Ciprofloxacin for 7 days is the therapy of choice.
D. If the *Campylobacter* subtype is *jejuni*, the patient should be monitored closely for systemic infection and distal organ involvement (seeding).
E. The *Campylobacter* subtype fetus carries a more favorable prognosis than other subtypes.

III-134. You are leading a medical aid team in a country in Central Africa when a cholera epidemic strikes a nearby village. As you ride to the village to assist in caring for the ill, one of the medical students on your team asks what causes the severe diarrhea. Which of the following statements regarding diarrhea in cholera is true?

A. Cholera toxin causes a disruption in the adenylate cyclase pathway in the intestinal epithelial cells.
B. Diarrhea in cholera is due to massive neutrophilic colonic inflammation.
C. Diarrhea due to cholera occurs due to an inability of the intestine to absorb glucose.
D. Fever often precedes the onset of diarrhea in cholera.
E. The stool in cholera diarrhea is often dark brown or black.

III-135. While you are caring for villagers stricken with cholera in Central Africa, you encounter Mr. Zi, a 22-year-old truck driver with cholera. He has the typical rice-water stools and has had seven bowel movements today before noon. He is thirsty but is able to hold a coherent conversation with you and can stand up without feeling lightheaded. His heart rate is 87 beats/min, and blood pressure is 105/70. Which of the following is the most appropriate treatment for Mr. Zi?

A. Erythromycin 250 mg orally four times daily for 3 days
B. IV fluid replacement with normal saline 100 mL/kg over 3 hours
C. IV fluid replacement with lactated Ringer's solution 100 mg/kg over 3 hours
D. Mix 0.5 teaspoon of table salt and 6 teaspoons of table sugar with 1 L of sterile water and have the patient drink up to 2 L of this solution daily
E. No treatment is necessary

III-136. A 52-year-old man with a past medical history of alcoholic cirrhosis presents in September, 2 days after eating a meal of raw oysters harvested from Virginia coastal waters, with 1 day of fever and chills. On examination, he appears acutely ill. He has a temperature of 39°C, a blood pressure of 78/59, a heart rate of 110 beats/min, and an oxygen saturation of 95% on room air. He has multiple erythematous patches on his lower legs. His labs show a low white blood cell count. Which of the following organisms is the most likely cause of his sepsis?

A. *Campylobacter jejuni*
B. *Escherichia coli* O157:H7
C. *Salmonella enteritidis*
D. *Shigella flexneri*
E. *Vibrio vulnificus*

III-137. Mr. Hsu is a 56-year-old former pig farmer from China who has been in the United States for the past year. Shortly after arriving, he began experiencing fevers. He did not seek medical attention because he had no insurance at the time and never felt that sick. Curiously, he has noted that while the fevers have persisted for a year they have not been continuous but have followed an unusual undulating pattern. The fever would usually last for 2 weeks and then relent for about 2 weeks at a time before returning. He also experienced joint pains and myalgias during his times of fever. More recently, he has experienced lower back pain with movement and at rest. He denies any weakness or numbness. A serologic investigation returns positive for IgG antibodies for *Brucella*. Which of the following statements regarding his condition is true?

A. A safe and effective human vaccine is available for brucellosis.
B. In this patient, *Brucella melitensis* is more likely than *B. suis*.
C. Prior to starting treatment, co-infection with tuberculosis should be excluded.
D. The presence of IgG antibodies is nonspecific. Given the atypical presentation, this likely is not a true *Brucella* infection.
E. With appropriate treatment, the patient's relapse rate from his disease is 1–2%.

III-138. A 30-year-old man presents in September with fevers, headaches, and muscle pains. He lives in Missouri. He had recently been on a hunting trip where he shot and skinned rabbits. A few days later, he developed an ulcer on his hand. Over the past few days, there was redness and pain surrounding the ulcer, and pain and swelling in his elbow. His vital signs are as follows: blood pressure 110/65, heart rate 110 beats/min, respiratory rate 24 breaths/min, and temperature 38.7°C. His oxygen saturation is 93% on room air. He appears mildly tachypneic and flushed. His conjunctiva are not injected, and his mucous membranes are dry. The chest examination reveals crackles in the left lower lobe. His heart rate is tachycardic but regular. There is a II/VI systolic ejection murmur heard best at the lower left sternal border. His abdominal examination is unremarkable. On the right hand, there is an erythematous ulcer with a punched-out center covered by a black eschar. He has no cervical lymphadenopathy, but there are markedly enlarged and tender lymph nodes in the right axillae and epitrochlear regions. Which of the following is the most appropriate therapy for this patient?

A. Ceftriaxone
B. Ciprofloxacin
C. Doxycycline
D. Gentamicin
E. Piperacillin-tazobactam

III-139. You are a physician in northern Arizona when there is an outbreak of *Yersinia pestis*. Which of the following is the most likely cause of the outbreak?

A. Bite from infected animal
B. Consumption of bear meat
C. Direct handling of prairie dogs
D. Fleabite
E. Person-to-person contact

III-140. You are seeing a 19-year-old undergraduate student in your office in northern New Mexico for left axillary pain. During the current summer break, he is assisting one of his university professors in research that involves trapping, tagging, and releasing prairie dogs. Today, he presents with fever (38.7°C), malaise, myalgias, and exquisite left axillary pain. On examination, he is uncomfortable, and his left axilla has a tender swelling with a boggy consistency and a hard core. There is an eschar in the patient's left upper abdominal quadrant (Figure III-140A). Gram stain of an aspirate of this swelling is shown in Figure III-140B. Which of the following organisms is responsible for this patient's infection?

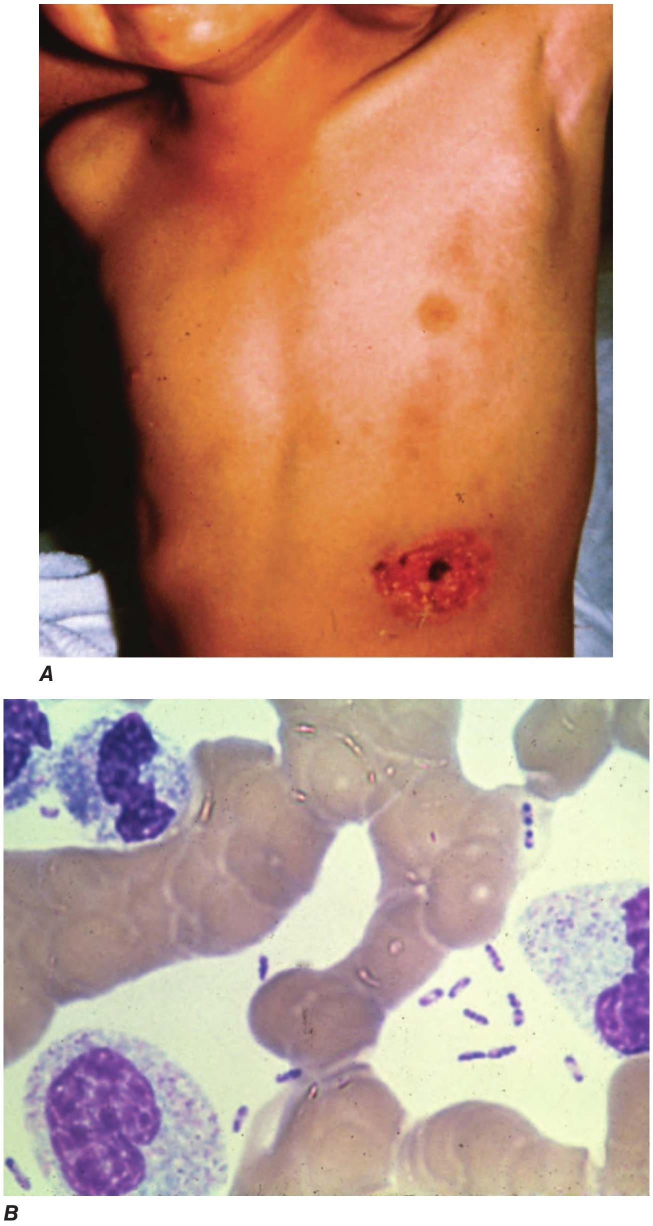


FIGURE III-140 Reproduced with permission from Fauci AS et al: *Harrison's Principles of Internal Medicine*, 17th ed. New York: McGraw Hill, 2008.

A. *Clostridium gangrenosum*
B. *Pseudomonas aeruginosa*
C. *Rhizopus arrhizus*
D. *Staphylococcus aureus*
E. *Yersinia pestis*

III-141. You are caring for a 15-year-old student who presented to the emergency department with left lower quadrant pain yesterday. Given his presentation, he was taken emergently to the operating room for an appendectomy. However, on exploratory laparotomy, his appendix appeared quite normal, and the surgeon visualized striking mesenteric adenitis and terminal ileitis. The operation was aborted without further intervention, and he was admitted to the medical intensive care unit. On further questioning, the patient endorsed eating chitterlings at a barbeque a week prior. You suspect his infection is due to which of the following?

A. *Clostridium difficile*
B. *Escherichia coli*
C. *Staphylococcus aureus*
D. *Trichinella spiralis*
E. *Yersinia enterocolitica*

III-142. All of the following statements regarding *Bartonella* endocarditis are true EXCEPT:

A. Homelessness and alcoholism are risk factors for *B. quintana* endocarditis.
B. *B. henselae* endocarditis is typically associated with exposure to cats.
C. With use of special culturing techniques, blood cultures are usually positive for *Bartonella* in *Bartonella* endocarditis.
D. Serologic tests are helpful in the diagnosis of *Bartonella* endocarditis.
E. Patients may have symptoms for months prior to a diagnosis of *Bartonella* endocarditis.

III-143. Mr. Sissen is a 40-year-old automobile mechanic. Two weeks ago he went to a local "minute-clinic" after a cat bite on his right ring finger. The wound was irrigated, and he was sent home with instructions for local wound care. Today, he presents to your clinic with 2 days of right axillary swelling (Figure III-143). His temperature is 38.4°C, and he has complained of general malaise over the past few days. You palpate no other lymphadenopathy on examination, and his finger has healed nicely without signs of overlying infection. He has no visual or neurologic complaints or abnormalities on examination. Which of the following is the most appropriate course of action?

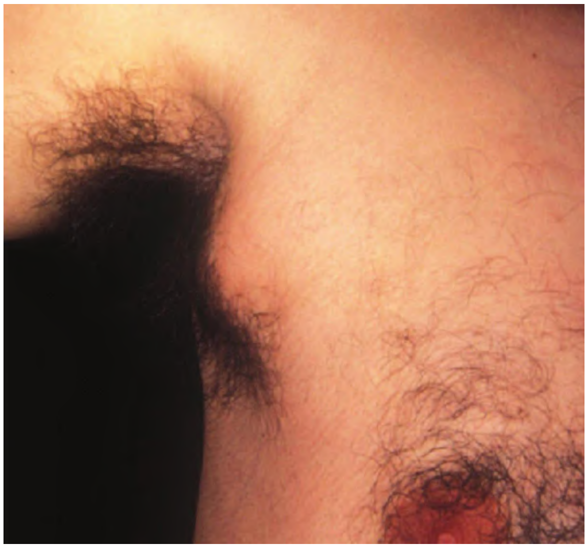


FIGURE III-143

A. Admit for blood cultures and empirically initiate vancomycin IV.
B. Check *Bartonella* serologies, electrolytes, and liver and renal function tests; do not initiate antibiotics.
C. Initiate azithromycin for a 5-day course.
D. Obtain peripheral blood thick and thin blood smears.
E. Refer for bone marrow aspirate and flow cytometry.

III-144. Mr. Pelosa is a 42-year-old man with HIV who is not on antiretroviral therapy and has a recent CD4 cell count of 43/μL. He presents with several nontender red, ulcerated plaques (Figure III-144). He endorses a couple of weeks of fever and malaise. Pathologic examination of a biopsy of one of the lesions reveals lobular proliferations of small blood vessels lined by enlarged endothelial cells interspersed with mixed infiltrates of neutrophils and lymphocytes. Blood cultures are positive for *Bartonella henselae*. What condition is causing the patient's skin lesions?

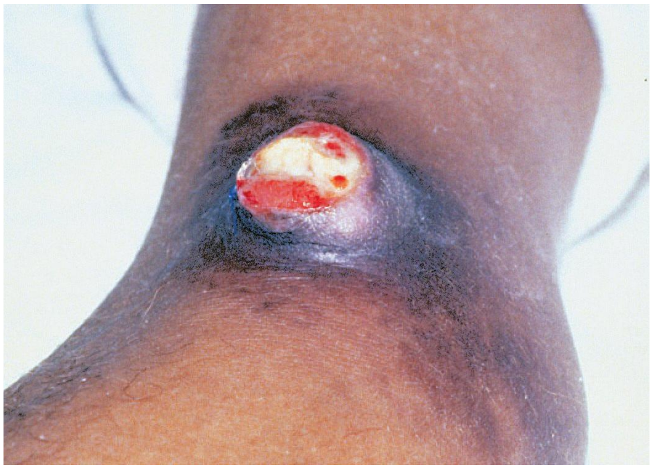


FIGURE III-144 Reproduced with permission from Fauci AS et al: Harrison's Principles of Internal Medicine, 17th ed. New York: McGraw Hill, 2008.

A. Bacillary angiomatosis
B. Bubonic plague
C. Kaposi sarcoma
D. Pyoderma gangrenosum
E. Verruga peruana

III-145. You see a 45-year-old immigrant from the Dominican Republic for a penile lesion (Figure III-145A). He has had no fevers or chills. He has had multiple sex partners over the last year. A Giemsa stain of the material is performed (Figure III-145B). Which of the following organisms is causing his infection?

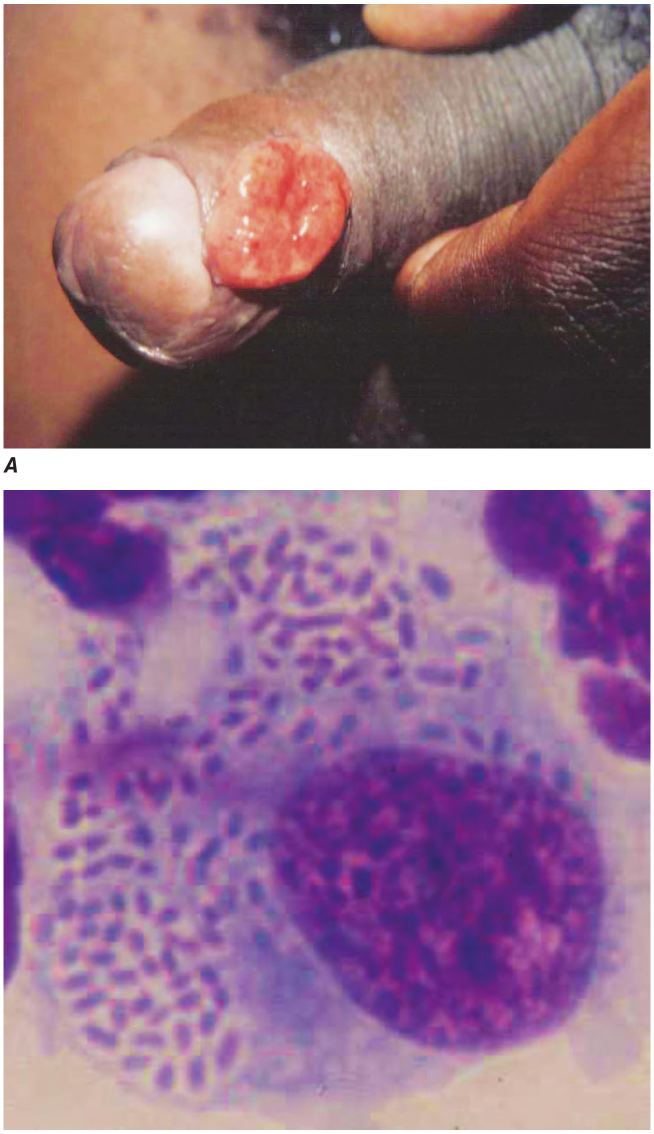


FIGURE III-145

A. *Chlamydia trachomatis*
B. *Haemophilus ducreyi*
C. *Klebsiella granulomatis*
D. *Treponema pallidum*
E. *Neisseria gonorrhea*

III-146. A 35-year-old man is seen 6 months after a cadaveric renal allograft. The patient has been on tacrolimus and prednisone since that procedure. He has felt poorly for the past 2 weeks with fever to 38.6°C (101.5°F), anorexia, and a cough productive of thick sputum. Chest x-ray reveals a left lower lobe (5-cm) mass with central cavitation. Examination of the sputum reveals long, crooked, branching, beaded gram-positive filaments. The sputum is also weakly acid-fast on a smear (Figure III-146). The most appropriate initial therapy would include the administration of which of the following antibiotics?

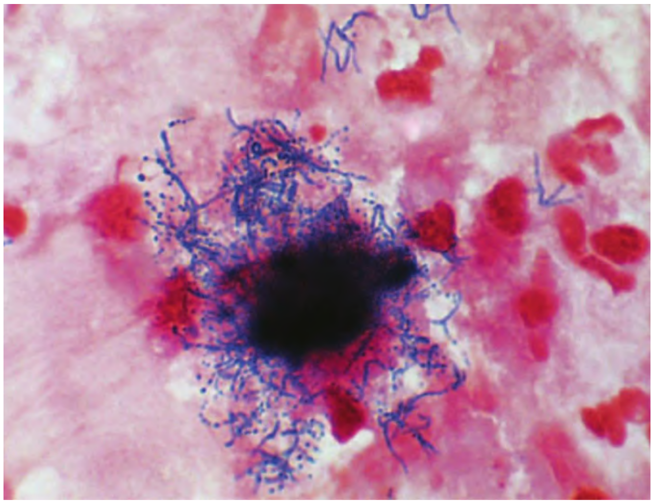


FIGURE III-146 Used with permission from Charles Cartwright and Susan Nelson, Hennepin County Medical Center, Minneapolis, MN.

A. Ceftazidime
B. Erythromycin
C. Penicillin
D. Tobramycin
E. Trimethoprim-sulfamethoxazole

III-147. A 52-year-old woman with a history of homelessness presents with several months of a slowly growing tender firm mass in her right jaw. Over the last week there has been an area of yellow purulent drainage through the buccal mucosa, and she has developed a fever. She is taken to surgery for removal of the mass. Which of the following is microscopic examination of the purulent secretions most likely to show?

A. Auer rods
B. Sialolith
C. Squamous cell carcinoma
D. Sulfur granules
E. Weakly acid-fast branching, beaded filamentous rods

III-148. In the patient described in question III-147, which of the following is the most appropriate therapy?

A. All trans-retinoic acid with arsenic trioxide
B. Penicillin
C. Removal of obstructing mass
D. Surgical debridement
E. Trimethoprim-sulfamethoxazole

III-149. A 52-year-old man presents with a year of watery diarrhea and weight loss. Workup reveals anemia and hypereosinophilia. CT imaging of his abdomen shows retroperitoneal lymphadenopathy. As part of his workup upper endoscopy is performed. Histology findings of a duodenal biopsy show infiltration of the lamina propria with macrophages containing periodic acid–Schiff stain-positive inclusions. All of the following statements regarding his condition are true EXCEPT:

A. Central nervous system disease can occur in 50% of patients.
B. Exposure to the infected agent rarely results in disease.
C. It may also cause culture-negative endocarditis.
D. Mesenteric and retroperitoneal lymphadenopathy are common.
E. This infection can be treated with a 2-week course of vancomycin.

III-150. A 68-year-old homeless man with a long history of alcohol abuse presents to his primary care physician with several weeks of fever, night sweats, and sputum production. He denies nausea, vomiting, or other gastrointestinal symptoms. Examination is notable for low-grade temperature, weight loss of 15 lb since the last visit, and foul breath; otherwise, it is normal. Blood work, including complete blood count and serum chemistries, is unremarkable. An interferon-γ release assay is negative. His chest radiograph is shown in Figure III-150. Which of the following is most appropriate as the initial intervention?

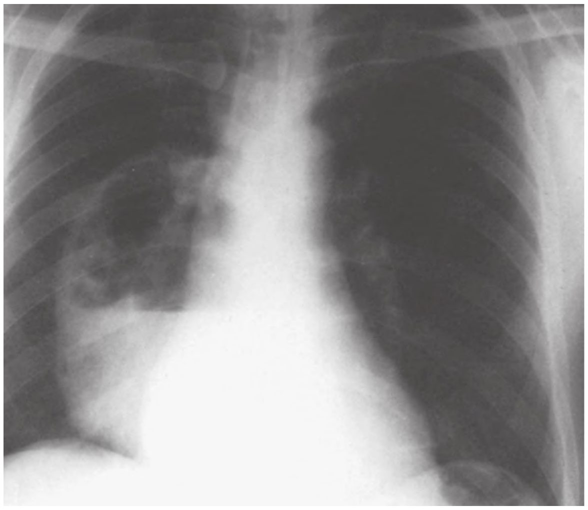


FIGURE III-150 Reproduced with permission from Mandell GL: *Atlas of Infectious Diseases*, Vol VI. Philadelphia: Current Medicine Inc, Churchill Livingstone, 1996.

A. Bronchoscopy with biopsy of the cavity to diagnose squamous cell lung cancer
B. Esophagogastroduodenoscopy to diagnose hiatal hernia with aspiration
C. Immediate hospitalization and isolation to prevent spread of Mycobacterium tuberculosis
D. IV ampicillin-sulbactam for lung abscess
E. IV meropenem for lung abscess

III-151. Which of the following statements regarding infections with anaerobic bacteria is true?

A. Anaerobes colonizing mucosal sites typically cause infections of mucosal sites.
B. Monomicrobial anaerobic infections are typical.
C. Most infections with anaerobic bacteria have a putrid smell.
D. Purely anaerobic infections frequently lead to sepsis.
E. Trauma and necrosis favor the growth of anaerobic bacteria.

III-152. All of the following factors influence the likelihood of transmitting active tuberculosis EXCEPT:

A. Duration of contact with an infected person
B. Environment in which contact occurs
C. Presence of extrapulmonary tuberculosis
D. Presence of laryngeal tuberculosis
E. Probability of contact with an infectious person

III-153. All of the following individuals should be screened for latent tuberculosis infection with the exception of which?

A. A 66-year-old woman with psoriatic arthritis who will be starting etanercept.
B. The 34-year-old spouse of a patient diagnosed with pulmonary tuberculosis
C. A 48-year-old schoolteacher with no past medical history
D. A 23-year-old male recently diagnosed with HIV
E. A 70-year-old patient diagnosed with silicosis

III-154. A 42-year-old Nigerian man comes to the emergency department because of fevers, fatigue, weight loss, and cough for 3 weeks. He complains of fevers and a 4.5-kg weight loss. He describes his sputum as yellow in color. It has rarely been blood streaked. He emigrated to the United States 1 year ago and is an undocumented alien. He has never been treated for tuberculosis, has never had a purified protein derivative (PPD) skin test placed, and does not recall receiving bacillus Calmette-Guérin vaccination. He denies HIV risk factors. He is married and reports no ill contacts. He smokes a pack of cigarettes daily and drinks a pint of vodka on a daily basis. On physical examination, he appears chronically ill with temporal wasting. His body mass index is 21 kg/m^2. Vital signs are as follows: blood pressure 122/68, heart rate 89 beats/min, respiratory rate 22 breaths/min, SaO_2 95% on room air, and temperature 37.9°C. There are amphoric breath sounds posteriorly in the right upper lung field with a few scattered crackles in this area. No clubbing is present. The examination is otherwise unremarkable. His chest radiograph is shown in Figure III-154. A stain for acid-fast bacilli is negative. What is the most appropriate approach to the ongoing care of this patient?

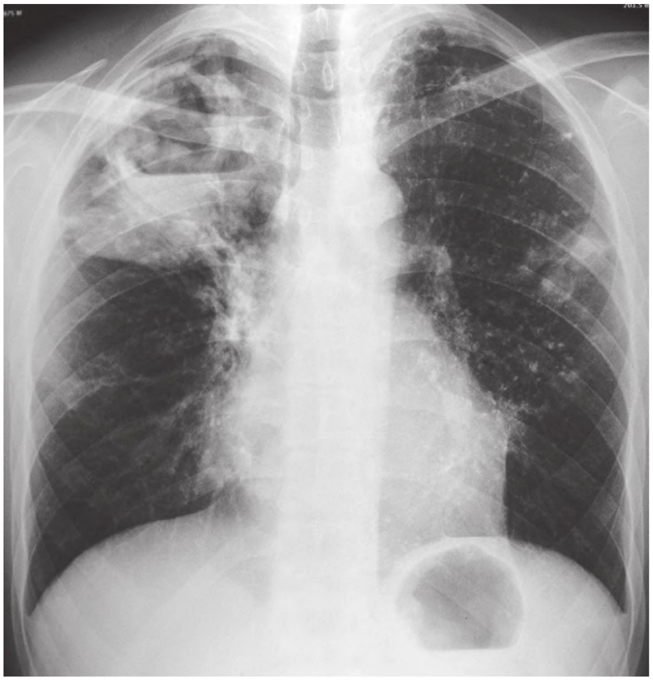


FIGURE III-154 Used with permission from Dr. Andrea Gori, Infectious Diseases Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy.

A. Admit the patient on airborne isolation until three expectorated sputum specimens show no evidence of acid-fast bacilli.
B. Admit the patient without isolation as he is unlikely to be infectious with a negative acid-fast smear.
C. Perform a biopsy of the lesion and consult oncology.
D. Place a PPD test on his forearm and have him return for evaluation in 3 days.
E. Start a 6-week course of antibiotic treatment for anaerobic bacterial abscess.

III-155. A 54-year-old immigrant from India presents with 1 month of progressive malaise, weight loss, night sweats, and low-grade fevers, but no cough or sputum production. He does have a history of untreated HIV. A chest x-ray is taken and is shown in Figure III-155. Which of the following forms of tuberculosis is he most likely to have?

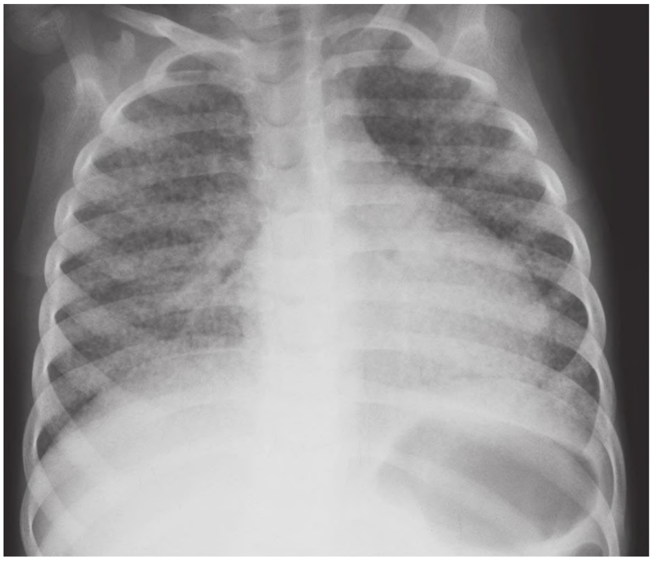


FIGURE III-155 Used with permission from Prof. Robert Gie, Department of Paediatrics and Child Health, Stellenbosch University, South Africa.

A. Disseminated
B. Extrapulmonary
C. Lymphadenitis
D. Pleural
E. Postprimary cavitary

III-156. A 30-year-old man is admitted to the hospital for active pulmonary tuberculosis with a positive sputum acid-fast bacilli smear. He is HIV positive with a CD4 count of 45/μL and is not on highly active antiretroviral therapy. Which of the following is the most appropriate initial therapy?

A. Isoniazid, rifampin, ethambutol, and pyrazinamide alone
B. Isoniazid, rifampin, ethambutol, and pyrazinamide; initiate antiretroviral therapy within 2 weeks
C. Isoniazid, rifampin, ethambutol, pyrazinamide, and streptomycin
D. Isoniazid, rifampin, and ethambutol
E. Withhold therapy until sensitivities are available

III-157. All of the following individuals receiving tuberculin skin purified protein derivative (PPD) reactions should be treated for latent tuberculosis EXCEPT:

A. A 23-year-old injection drug user who is HIV negative and has a 12-mm PPD reaction.
B. A 38-year-old fourth grade teacher who has a 7-mm PPD reaction and no known exposures to active

tuberculosis; she has never been tested with a PPD previously.

C. A 43-year-old individual in the Peace Corps working in sub-Saharan Africa who has a 10-mm PPD reaction; 18 months ago, the PPD reaction was 3 mm.

D. A 55-year-old man who is HIV positive and has a negative PPD; his partner was recently diagnosed with cavitary tuberculosis.

E. A 72-year-old man who is receiving chemotherapy for non-Hodgkin lymphoma and has a 16-mm PPD reaction.

III-158. All of the following statements regarding interferon-γ release assays (IGRAs) for the diagnosis of latent tuberculosis are true EXCEPT:

A. IGRAs are more specific than tuberculin skin testing.

B. There is no loss in sensitivity for patients with immunocompromising conditions with these assays.

C. These assays are preferred for latent tuberculosis testing in low-incidence, high-income settings.

D. These assays have less cross-reactivity with bacillus Calmette-Guérin and nontuberculous mycobacteria than tuberculin skin testing.

E. These assays measure T-cell release of interferon-γ in response to stimulation with tuberculosis-specific antigens.

III-159. All of the following statements regarding bacillus Calmette-Guérin (BCG) vaccination are true EXCEPT:

A. BCG dissemination may occur in severely immunosuppressed patients.

B. BCG vaccination is recommended at birth in countries with high tuberculosis (TB) prevalence.

C. BCG vaccination may cause a false-positive tuberculin skin test.

D. BCG vaccine provides protection for infants and children from TB meningitis and miliary disease.

E. BCG vaccine provides protection from TB in HIV-infected patients.

III-160. A 50-year-old man who moved from India 2 years ago presents with 6 months of two hypopigmented plaques on his arms that are sharply demarcated and hypesthetic (Figure III-160). He has had these treated with topical steroids but the plaques did not improve. A biopsy is obtained of the edge of the lesion, and it shows that T cells have invaded the peripheral nerves in the dermis. Which of the following statements regarding his condition is true?

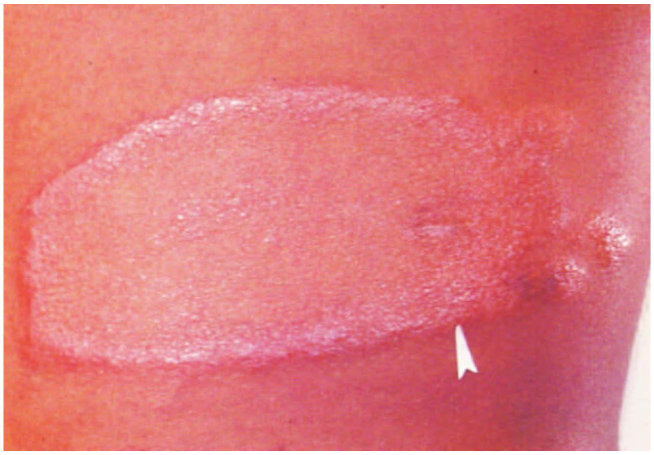


FIGURE III-160

A. His disease is more consistent with tuberculoid leprosy than lepromatous leprosy.

B. The incubation period for this disease is 1 year.

C. The central nervous system is often involved.

D. The central part of the lesion has the highest sensitivity for the diagnosis.

E. Treatment is with rifampin and isoniazid.

III-161. A thin 76-year-old woman presents with 4 months of chronic nonproductive cough, at times leading to posttussive emesis. She has had progressive weight loss of 10 lb over this time period. She does have a past medical history of pneumonia that was treated when she was 50. A chest CT is performed (Figure III-161). Three separate sputum samples are obtained and sent for acid-fast bacilli. Six weeks later, each grow *Mycobacterium avium* complex. Which of the following regimens is most likely to cure her infection?

A. Aggressive pulmonary toilet

B. Azithromycin, ethambutol, and rifampin for 12 months

C. Clarithromycin and rifampin for 6 months

D. Moxifloxacin, ethambutol, and rifampin for 12 months

E. Pyrazinamide, isoniazid, rifampin, and ethambutol for 2 months followed by isoniazid and rifampin for 4 months

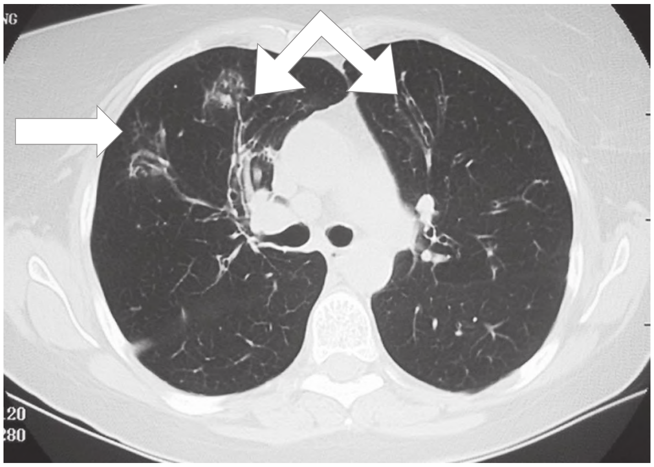


FIGURE III-161

III-162. A 45-year-old patient with HIV/AIDS presents to the emergency department. He complains of a rash that has been slowly spreading up his right arm and is now evident on his chest and back. The rash consists of small nodules that have a reddish-blue appearance. Some of them are ulcerated, but there is minimal fluctuance or drainage. He is unsure when these began. He notes no foreign travel or unusual exposures. He is homeless and unemployed but occasionally gets work as a day laborer doing landscaping and digging. Culture of a skin lesion grows *Mycobacterium* in 5 days. Which of the following is the most likely organism?

A. *M. abscessus*
B. *M. avium*
C. *M. kansasii*
D. *M. marinum*
E. *M. ulcerans*

III-163. All of the following statements regarding antituberculosis therapeutic agents are true EXCEPT:

A. In the United States, *Mycobacterium tuberculosis* resistance to isoniazid remains <10%.
B. Optic neuritis is the most severe adverse effect of ethambutol.
C. Pyrazinamide has utility in the therapy of *Mycobacterium avium* complex and *Mycobacterium kansasii* infections.
D. Rifabutin should be used instead of rifampin in patients receiving concurrent treatment with protease inhibitors or nevirapine.
E. Rifampin can decrease the half-life of warfarin, cyclosporine, prednisone, oral contraceptives, clarithromycin, and other important drugs.

III-164. A 22-year-old college student presents for the evaluation of a painless nonpruritic rash of 1-week duration. Three months ago he engaged in unprotected sexual intercourse. Two months ago he noted a penile papule that evolved to a painless, clean-based, and indurated ulcer. He did not seek medical attention because the ulcer healed spontaneously. Subsequently, he developed the maculopapular rash pictured in Figure III-164 involving his trunk, as well as painless papules on his palms and soles of the feet. He complains of no other symptoms and has no stigmata of ocular or neurologic involvement. He reports no new medications and has no known drug allergies. He does not have HIV. Which of the following is the most appropriate antibiotic regimen?

A. Azithromycin 1000 mg orally for one dose
B. Benzathine penicillin G 2.4 mU IM for one dose
C. Doxycycline 100 mg orally twice a day for 14 days
D. Doxycycline 200 mg orally for one dose
E. Penicillin G 18–24 mU/d IV for 14 days

III-165. A 68-year-old man is referred for evaluation of gait instability. He complains of lightning-like pains lancinating to his thighs that last minutes. Examination is notable for impaired proprioception and vibratory sense in his feet. He has a wide-based, ataxic gait and a positive Romberg sign. He has a history of multiple episodes of unprotected sex 30–40 years ago. He could also have all of the following physical findings EXCEPT:

A. Pupils that react to accommodation but not light.
B. Pupils that react to light but not accommodation
C. Decreased temperature sensation
D. Impaired short-term memory
E. Areflexia

III-166. A 74-year-old woman with mild cognitive impairment is screened for syphilis. She has no history of recent sexual activity or of prior exposure to syphilis. The prevalence of syphilis in her local population is low. Her rapid plasma reagin (RPR) is reactive with a titer of ≤1:2. Her fluorescent treponemal antibody absorption test is nonreactive. The reactive RPR is most likely:

A. False negative because the nontreponemal test is negative
B. False negative because the treponemal test is positive
C. False positive because the nontreponemal test is negative
D. False positive because the treponemal test is negative
E. True positive because the nontreponemal test is positive

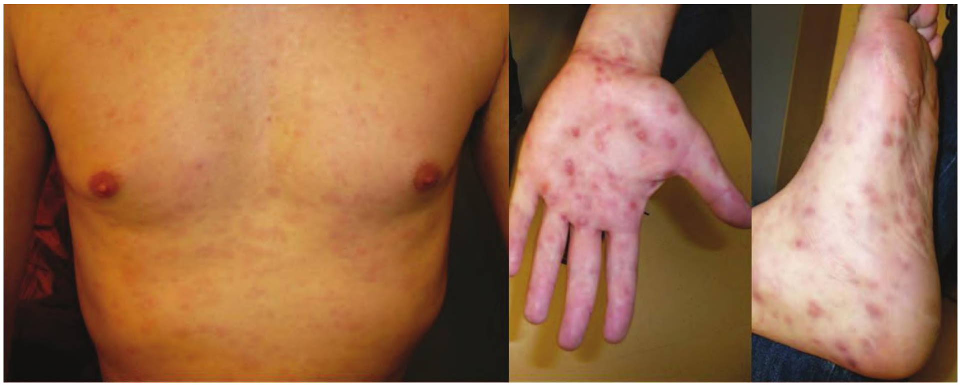


FIGURE III-164 Used with permission from Jill McKenzie and Christina Marra.

III-167. A 43-year-old male with HIV, on treatment with an undetectable viral load and a CD4 cell count of 263, presents for evaluation of visual changes over the last month. On examination, he is noted to have uveitis, but normal temperature sensation, proprioception, deep pain sensation, reflexes, and gait. Which of the following tests should you do next?

A. Lumbar puncture for bacterial cultures, cell counts, protein, and glucose.
B. Lumbar puncture for rapid plasma reagin (RPR), cell counts, protein, and glucose and serum for RPR
C. Lumbar puncture for VDRL, cell counts, protein, and glucose and serum for RPR
D. MRI of the brain
E. Serum for RPR and VDRL

III-168. For the patient described in question III-167, assuming the test you ordered is positive, which of the following is the appropriate treatment for his condition?

A. Aqueous crystalline penicillin G 24 million units IV daily (continuous infusion) for 14 days
B. Benzathine penicillin G 24 million units IV daily for 14 days
C. Benzathine penicillin G 2.4 million units IM weekly for 4 weeks
D. Ceftriaxone 2 g IV daily for 7 days
E. Doxycycline 100 mg PO twice daily for 14 days

III-169. All of the following are indications for cerebrospinal fluid examination in adults infected with syphilis EXCEPT:

A. HIV infection with CD4+ count ≤ 350/μL
B. Maculopapular rash involving the palms and soles
C. RPR titer ≥1:32
D. Sensorineural hearing loss
E. Suspected treatment failure

III-170. A 21-year-old woman originally from Papua New Guinea presents with 6 months of an ulcer on her right leg (Figure III-170). The ulcer has almost healed, but she now has generalized lymphadenopathy most pronounced in her inguinal lymph nodes and then multiple papules near the site of the ulcer (Figure III-170). Which of the following should you use to treat her infection?

A. Azithromycin
B. Rifampin, isoniazid, pyrazinamide, and ethambutol
C. Dapsone and rifampicin
D. Parenteral vancomycin
E. Piperacillin-tazobactam

III-171. Mr. Viper is a 52-year-old man who presents for evaluation of fever and jaundice. Flu-like symptoms including fever, chills, headache, and myalgias started suddenly 2 days ago. Yesterday, he noted scleral icterus and darkened urine. Today, he developed new cough, chest discomfort, dyspnea, and hemoptysis. He resides in Baltimore City and works as an exterminator. Two weeks ago, he suffered a minor leg injury while working in a home plagued with standing water and rats. He has no other travel or exposure history. Which pattern of electrolytes is typical of acute kidney injury in the severe form of this spirochetal zoonosis?

A. Hyperkalemia and hyponatremia
B. Hyperkalemia and hypernatremia
C. Hypokalemia and hyponatremia
D. Hypokalemia and hypernatremia

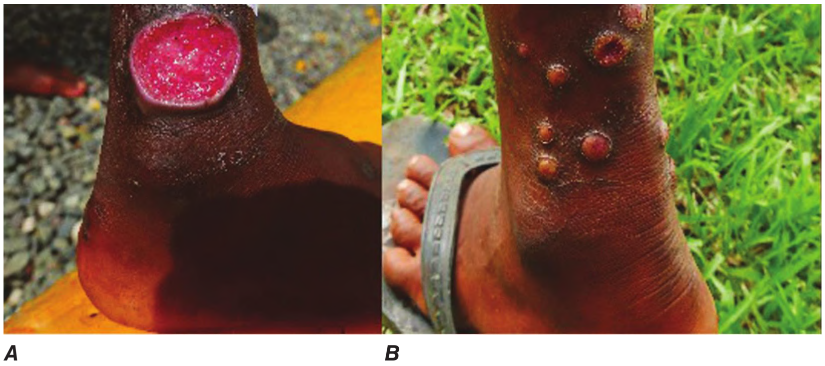


FIGURE III-170 Used with permission from Dr. Oriol Mitjà.

III-172. A 23-year-old man with no past medical history was on a camping trip in Glacier National Park 3 weeks ago. He was careful to sterilize his water and not eat or drink any unpasteurized milk products. He did not notice any rodent droppings. He did have several insect bites and pulled a tick off himself. He has had fevers over 40°C with myalgias, headache, nausea, vomiting, and diarrhea starting 5 days after he returned home. The fevers went away after 3 days. Seven days later, the fevers returned including temperatures as high as 40°C, associated with intermittent confusion. The fevers subsided again after 3 days. A thin blood smear is examined and shown in Figure III-172. Which of the following is the most likely cause of the patient's recurrent fevers?

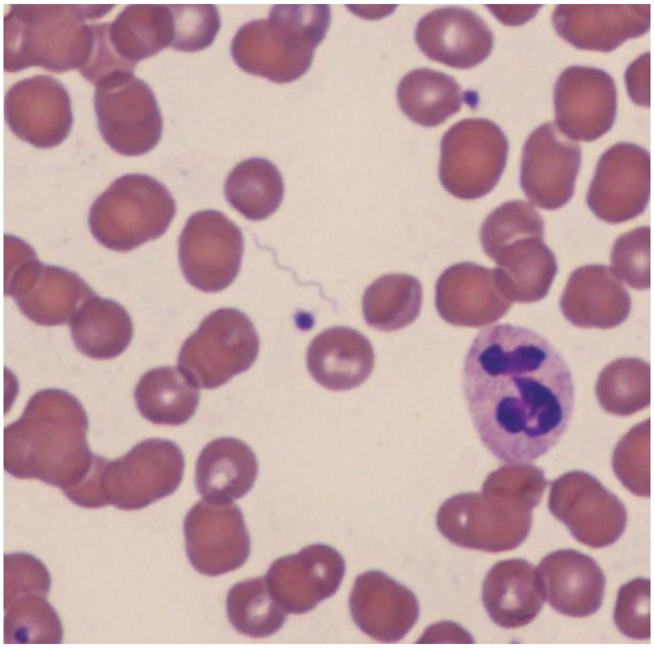


FIGURE III-172

A. Brucellosis
B. Colorado tick fever
C. Leptospirosis
D. Lymphocytic choriomeningitis
E. Tick-borne relapsing fever

III-173. Infection by which of the following organisms causes the rash shown in Figure III-173?

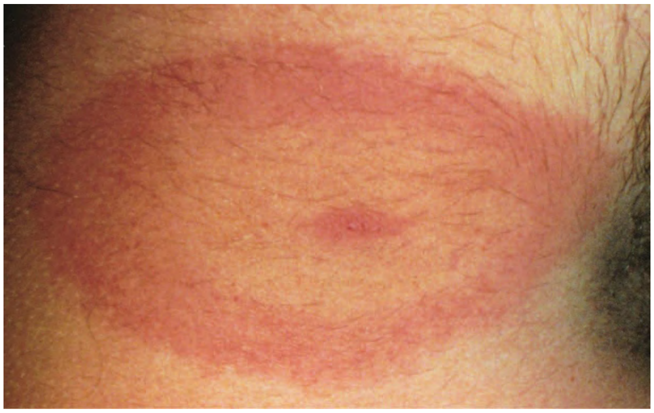


FIGURE III-173 Used with permission from Vijay K. Sikand, MD.

A. *Anaplasma phagocytophilum*
B. *Bartonella henselae*
C. *Borrelia burgdorferi*
D. *Ehrlichia chaffeensis*
E. *Rickettsia rickettsii*

III-174. A 42-year-old woman living in Connecticut during the summer presents to the emergency department with light-headedness and dizziness. She has a heart rate of 40 beats/min, and she has complete heart block on electrocardiogram. She states that she spends much of her time gardening and has found ticks on herself. Her father had an acute myocardial infarction at the age of 50. She is training for a marathon. She has no fevers. There are no abnormalities on physical examination, chemistry panel, or chest x-ray. Which of the following is the most likely cause of the complete heart block in this patient?

A. Acute myocardial infarction
B. Bacterial endocarditis
C. Chagas disease
D. Lyme disease
E. Sarcoidosis

III-175. *Borrelia burgdorferi* serology testing is indicated for which of the following patients, all of whom reside in Lyme-endemic regions?

A. A 19-year-old female camp counselor who presents with her second episode of an inflamed, red, and tender left knee and right ankle
B. A 23-year-old male house painter who presents with a primary erythema migrans lesion at the site of a witnessed tick bite
C. A 36-year-old female state park ranger who presents with a malar rash; diffuse arthralgias/arthritis of her shoulders, knees, and metacarpophalangeal and proximal interphalangeal joints; pericarditis; and acute glomerulonephritis
D. A 42-year-old woman with chronic fatigue, myalgias, and arthralgias
E. A 46-year-old male gardener who presents with fevers, malaise, migratory arthralgias/myalgias, and three erythema migrans lesions

III-176. A healthy 51-year-old New Jersey resident presents in September with one week of low-grade fevers, malaise, fatigue, headache, diffuse arthralgias, and a rash. He golfs every weekend with variable results, and often hits balls into the deep rough. On examination, he appears fatigued. His temperature is 38°C, pulse is 80 beats/min, blood pressure is 110/70, and respiratory rate is 16 breaths/min. On examination he has clear breath sounds, no cardiac rub or murmur, normal bowel sounds, no synovitis, and no organomegaly. Multiple erythema migrans lesions are found on skin examination. All of the following complications may be associated with his condition EXCEPT:

A. Atrioventricular block
B. Chronic diarrhea
C. Memory impairment
D. Oligoarticular arthritis
E. Peripheral neuropathy

III-177. In the patient described in question III-176, which of the following is the most appropriate therapy?

A. Amoxicillin 500 mg PO bid
B. Azithromycin 500 mg PO daily
C. Ceftriaxone 2 g IV daily
D. Doxycycline 100 mg PO bid
E. Vancomycin 1 g IV bid

III-178. A 32-year-old man is admitted to the intensive care unit in July with hypotension and fever. He lives in a suburban area of New Jersey. He became ill yesterday with a fever as high as 40°C (104°F). Today, his wife noted increasing confusion and lethargy. Over this same time, he has complained of headaches, myalgias, and nausea. Prior to the acute onset of illness, he had no medical complaints. He has no other medical history and takes no medications. He works in landscaping. On presentation, the vital signs are as follows: blood pressure 90/60, heart rate 130 beats/min, respiratory rate 22 breaths/min, temperature 39°C, and oxygen saturation 94% on room air. His physical examination reveals an ill-appearing man, moaning quietly. He is oriented to person only. His cardiac examination reveals a regular tachycardia. His chest and abdominal examinations are normal. He has no rash. His white blood cell count is 3.0 cells/μL, his platelet count is 50, and his aspartate aminotransferase and alanine aminotransferase are five times the upper limit of normal. A peripheral blood smear is performed and shown in Figure III-178. In addition to supportive care, which of the following medications should this patient receive?

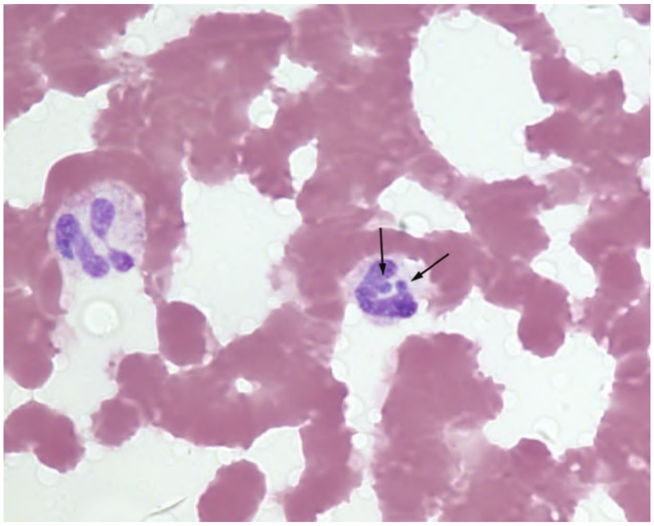


FIGURE III-178 Used with permission from Dr. J. Stephen Dumler.

A. Ceftriaxone 2 g IV daily
B. Doxycycline 100 mg PO bid
C. Ampicillin 2 g IV every 6 hours
D. Vancomycin IV
E. Levofloxacin 750 mg PO daily

III-179. A 27-year-old man who lives in North Carolina presents to his primary care physician complaining of fever, headache, myalgias, nausea, and anorexia 7 days after returning from hiking on the Appalachian Trail. Physical examination is remarkable for a temperature of 38.6°C (101.5°F). He appears generally fatigued but not toxic and does not have a rash. He is reassured by his primary care physician that this likely represents a viral illness, but he returns to the clinic 3 days later with a new progressive rash and ongoing fevers. He states that small red spots began to appear on the wrists and ankles within 24 hours of the prior visit and have now progressed up his extremities and onto the trunk (Figure III-179). He also notes an increasing headache, and his wife thinks he has had some confusion. On physical examination, the patient is noted to be lethargic and answers questions slowly. Which of the following would be the most reasonable course of action?

A. Admit the patient to the hospital for treatment with IV ceftriaxone 1 g bid and vancomycin 1 g bid
B. Admit the patient to the hospital for treatment with doxycycline 100 mg bid
C. Initiate treatment with doxycycline 100 mg PO bid as an outpatient
D. Initiate treatment with trimethoprim-sulfamethoxazole double strength twice daily
E. Order rickettsial serologies and withhold treatment until a firm diagnosis is made

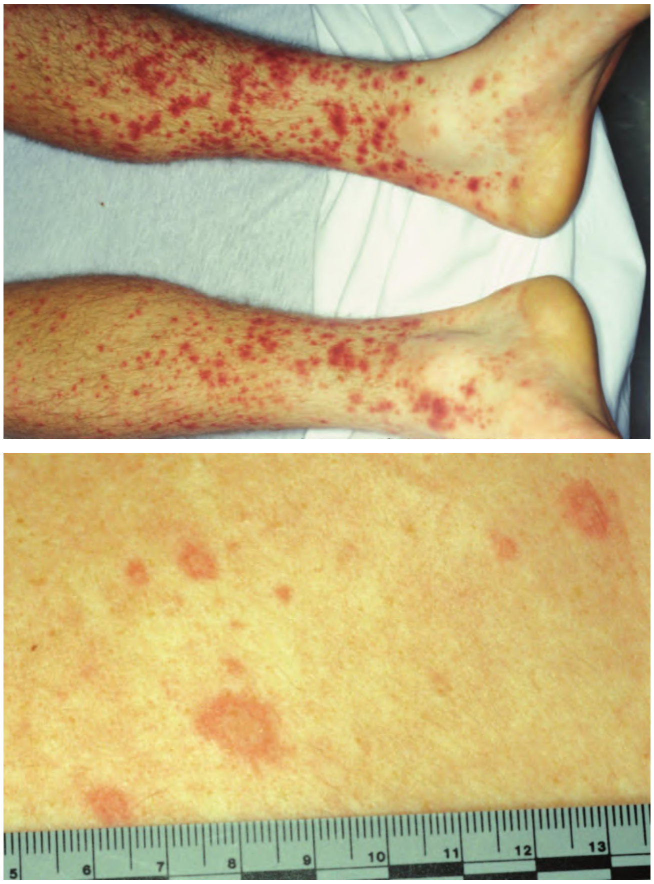


FIGURE III-179 Used with permission from Dr. Lindsey Baden.

III-180. A previously healthy 20-year-old college student presents with several days of headache, extensive cough with scant sputum, and fever of 38.6°C (101.5°F) in September. Several individuals in his dormitory have also been ill with a similar illness. On examination, pharyngeal erythema is noted, and lung examination reveals bilateral expiratory wheezing and scattered crackles in the lower lung zones. He coughs frequently during the examination. Chest radiograph reveals bilateral peribronchial pneumonia with increased interstitial markings. No lobar consolidation is seen. Which organism is most likely to cause the patient's presentation?

A. Adenovirus
B. *Chlamydophila pneumoniae*
C. *Legionella pneumophila*
D. *Mycoplasma pneumoniae*
E. *Streptococcus pneumoniae*

III-181. A 23-year-old man with no past medical history presents with 2 weeks of dysuria and urethral discharge. He has a history of unprotected insertive vaginal sex with multiple partners over the last 2 months. Polymerase chain reaction testing for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* is negative. On examination, there is a scant white discharge from the penile meatus but no lymphadenopathy, ulcers, or lesions are found. Which of the following is the most likely cause of his symptoms?

A. *C. trachomatis* serovar L1
B. Herpes simplex virus-1
C. Herpes simplex virus-2
D. *Treponema pallidum*
E. *Ureaplasma*

III-182. A 42-year-old woman is admitted to the intensive care unit with hypoxemic respiratory failure and pneumonia in August. She was well until 2 days prior to admission when she developed fevers, myalgias, and headache. She works in a poultry processing plant and is originally from El Salvador. She has been in the United States for 15 years. She has no major health problems. Her purified protein derivative was negative on arrival to the United States. Several other workers have been ill with a similar illness, although no one else has developed respiratory failure. She is currently intubated and sedated. Her oxygen saturation is 93% on an FiO_2 of 0.80 and positive end-expiratory pressure of 12 cm H_2O. On physical examination, crackles are present in both lung fields. There is no cardiac murmur. Hepatosplenomegaly is present. Laboratory studies reveal a mild transaminitis. Influenza nasal swab is negative for the presence of influenza A. Which of the following tests is most likely to be positive in this patient?

A. Acid-fast bacilli stain and mycobacterial culture for *Mycobacterium tuberculosis*
B. Blood cultures growing *Staphylococcus aureus*
C. Microimmunofluorescence testing for *Chlamydia psittaci*
D. Urine *Legionella* antigen
E. Viral cultures of bronchoscopic samples for influenza A

III-183. A 46-year-old male with well-controlled HIV on tenofovir-emtricitabine-bictegravir with an undetectable HIV viral load and a CD4 T-cell level of 600 cells/mm^3 presents with 3 weeks of anorectal pain, bloody mucopurulent discharge, tenesmus, fatigue, and low-grade fevers. There is no diarrhea or constipation. He has a history of unprotected receptive anal intercourse. On examination he has a temperature of 38°C and tender matted inguinal lymphadenopathy. A rectal examination had to be cut short due to significant tenderness on the prostate examination. A flexible sigmoidoscopy is performed and shows ulcerative proctitis, purulent exudate, and mucosal bleeding. Histopathologic findings of the rectal mucosa include granulomas with giant cells, crypt abscesses, and extensive inflammation. Nucleic acid amplification tests for *Chlamydia trachomatis* returns as positive. Which of the following is the most likely cause of his symptoms?

A. Crohn disease
B. Lymphogranuloma venereum
C. Gonococcus
D. Herpes simplex
E. Ulcerative colitis

III-184. A 21-year-old woman who is sexually active presents with 1 week of mild right lower abdominal pain, purulent vaginal discharge, painful intercourse, and bleeding after intercourse. On examination, she has a temperature of 38.5°C. On the pelvic examination, she has mild right-sided adnexal and uterine tenderness. She has mucopurulent endocervical exudate in the endocervical canal, followed by bleeding. Which of the following organisms is the most likely cause of her illness?

A. *Chlamydia trachomatis*
B. Group A *Streptococcus*
C. Herpes simplex virus-2
D. *Neisseria gonorrhoeae*

III-185. All of the following viruses can cause persistent or latent infections EXCEPT:

A. Hepatitis B virus
B. Hepatitis A virus
C. HIV
D. Human papillomavirus
E. Rabies virus

III-186. All of the following are correct associations between a virus and a malignancy it contributes to EXCEPT:

A. Hepatitis B virus: hepatocellular carcinoma
B. Human papillomavirus: anal cancer
C. Epstein-Barr virus: nasopharyngeal carcinoma
D. Herpes simplex virus: melanoma
E. Human herpesvirus-8 or Kaposi sarcoma-associated herpesvirus: multicentric Castleman syndrome

III-187. All of the following statements regarding herpes simplex virus (HSV) infection are true EXCEPT:

A. HSV-1 infection is usually acquired earlier in life than HSV-2 infection.
B. HSV-2 infection is a risk factor for HIV transmission.
C. Immunocompromised patients with defects in humoral immunity have more severe HSV infections than those with defects in cell-mediated immunity.
D. Most adults have antibodies to HSV-1.
E. Most patients infected with HSV-2 and HSV-1 have frequent subclinical bursts of reactivation lasting up to 4 hours.

III-188. A 33-year-old man with no other past medical history presents with myalgias, fatigue, and painful penile ulcers. One year ago when he had similar symptoms, a swab of one of the ulcers returned positive for herpes simplex virus-2 by polymerase chain reaction. Which of the following is the most appropriate treatment option for this patient?

A. Acyclovir 800 mg PO tid for 21 days
B. Famciclovir 125 mg PO bid for 14 days
C. Ganciclovir 1 g PO bid for 7 days
D. Valacyclovir 500 mg PO bid for 3 days
E. Valganciclovir 900 mg PO bid for 21 days

III-189. A 65-year-old man is brought to the hospital by his wife because of new-onset fever and confusion. He was well until 3 days ago, when he developed high fever, somnolence, and progressive confusion. His current medical history is unremarkable except for elevated cholesterol, and his only medication is atorvastatin. He is a civil engineer at an international construction company. His wife reports he obtains regular health screening and has always been purified protein derivative negative. On admission, his temperature is 40°C, and his vital signs are otherwise normal. He is confused and hallucinating. Soon after admission, he develops a tonic-clonic seizure that requires lorazepam to terminate. His head CT shows no acute bleeding or elevated intracranial pressure. An electroencephalogram shows an epileptiform focus in the left temporal lobe and diffusion-weighted MRI shows bilateral temporal lobe inflammation. Which of the following is most likely to be diagnostic?

A. Cerebrospinal fluid (CSF) acid-fast staining
B. CSF India ink stain
C. CSF polymerase chain reaction for herpes virus
D. CSF oligoclonal band testing
E. Serum cryptococcal antigen testing

III-190. All of the following patients are currently recommended to receive the recombinant zoster vaccine (Shingrix) EXCEPT:

A. A 52-year-old woman with a past medical history of hypertension who had chickenpox as a child
B. A 60-year-old man with no past medical history who cannot remember having had chickenpox in the past
C. A 73-year-old man with a past medical history of diabetes who had a negative screening test for antibodies to varicella-zoster virus
D. A 62-year-old male with a past medical history of chickenpox as a child who is on prednisone 15 mg daily to treat sarcoidosis
E. A 74-year-old woman who will soon be initiated on etanercept for rheumatoid arthritis

III-191. Mr. Brian is a 29-year-old man who comes to the emergency department complaining of a painful red rash on his leg, back, and buttocks that has worsened over the past 3 days. He reports it started as a few small red bumps but has grown and become more painful. His history is notable for HIV infection and medical noncompliance. He does not take any medications. He is afebrile, and his physical examination is unremarkable other than the rash shown in Figure III-191. Of note, the rest of his skin examination is unremarkable, and the painful rash does not cross the midline. Which of the following is the most effective treatment?

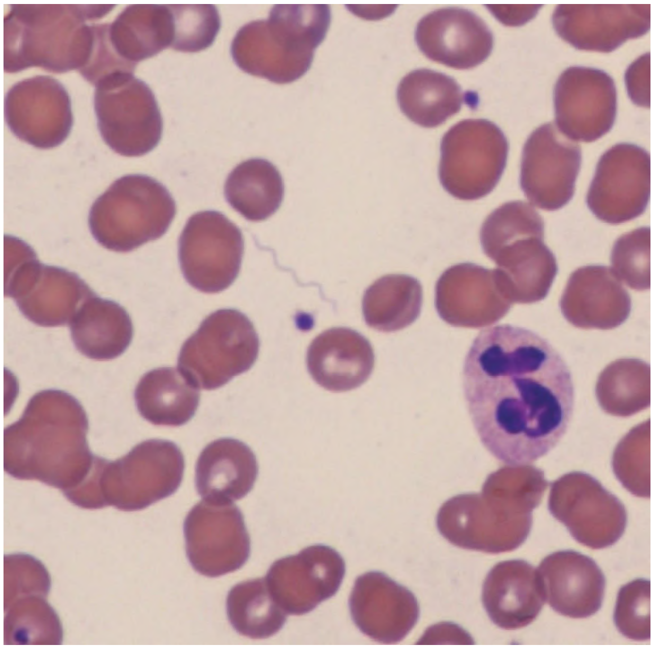


FIGURE III-191 Used with permission from Dr. Lindsey Baden.

A. Doxycycline
B. Ganciclovir
C. Penicillin
D. Piperacillin-tazobactam
E. Valacyclovir

III-192. A 19-year-old college student comes to the health clinic reporting that she has been ill for 2 weeks. At that time she developed notable fatigue and malaise that prevented her from her usual exercise regimen and caused her to miss some classes. Last week, she developed low-grade fevers, sore throat, and swollen lymph nodes in her neck. Her roommate gave her some amoxicillin that she had in her possession. Over the last 2 days, she has developed a worsening slightly itchy rash, as shown in Figure III-192. Her physical examination is notable for a temperature of 38.1°C, pharyngeal erythema, bilateral tonsillar enlargement without exudates, bilateral tender cervical adenopathy, and a palpable spleen. All of the following statements regarding her illness are true EXCEPT:

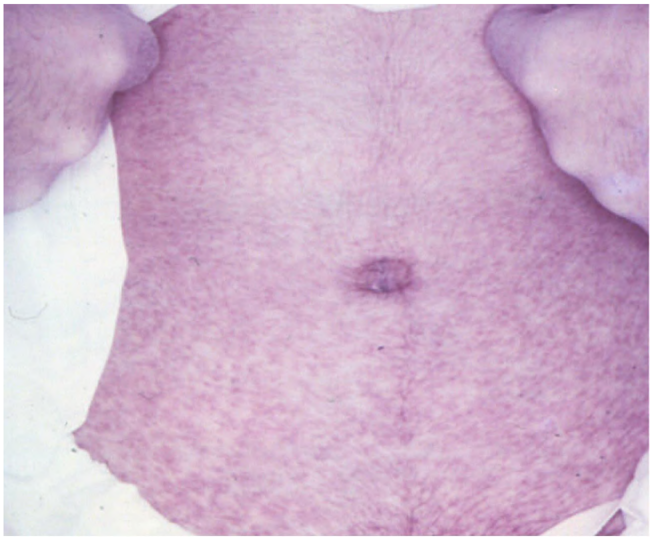


FIGURE III-192 Used with permission from Maria Turner, MD.

A. Greater than 10% atypical lymphocytosis is likely.
B. Heterophile antibody testing will likely be diagnostic.
C. If heterophile antibody testing is negative, testing for IgG antibodies against viral capsid antigen will likely be diagnostic.
D. It is spread via contaminated saliva.
E. The patient can receive amoxicillin in the future if indicated.

III-193. For the patient described in question III-192, which of the following is the indicated treatment?

A. Acyclovir
B. Acyclovir plus prednisone
C. Ganciclovir
D. Prednisone
E. Rest, supportive measures, and reassurance

III-194. Which of the following manifestations of cytomegalovirus (CMV) infection is the most likely to occur in patients with HIV and a CD4 <50 cells/mm?

A. CMV colitis
B. CMV hepatitis
C. CMV pneumonia
D. CMV retinitis
E. CMV syndrome (fever, malaise, cytopenias, transaminitis, and CMV viremia)

III-195. Which of the following serology patterns places a transplant recipient at the lowest risk of developing cytomegalovirus (CMV) infection after renal transplantation?

A. Donor CMV IgG negative, recipient CMV IgG negative.
B. Donor CMV IgG negative, recipient CMV IgG positive.
C. Donor CMV IgG positive, recipient CMV IgG negative.
D. Donor CMV IgG positive, recipient CMV IgG positive
E. The risk is equal regardless of serology results.

III-196. All of the following have been associated with human herpesvirus-8 EXCEPT:

A. Adult T-cell leukemia
B. B-cell body cavity–based lymphomas (primary effusion lymphomas)
C. Fever and a maculopapular rash in children
D. Kaposi sarcoma
E. Multicentric Castleman disease

III-197. A 35-year-old man with a past medical history of HIV, who is not on medications currently and has a CD4+ T-cell lymphocyte count of 126 cells/mL presents with 3 weeks of a rash on his upper right thigh. He describes the rash as "tiny bumps" that are nontender and do not itch. On examination, you see multiple small (2–5 mm) pearly, flesh-colored, umbilicated skin lesions on his upper right thigh (Figure III-197). Which of the following is the most likely diagnosis?

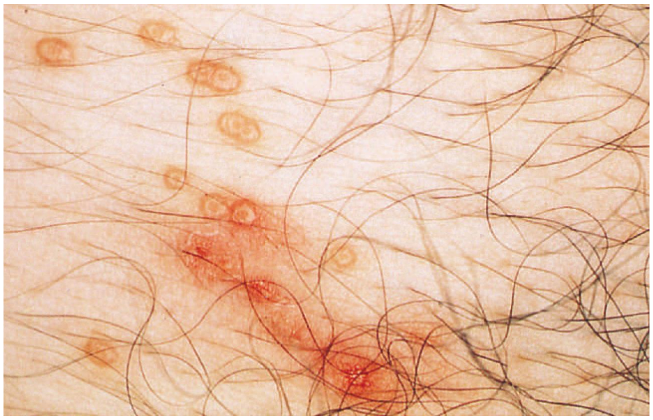


FIGURE III-197

A. Herpes simplex
B. Human papillomavirus
C. Molluscum contagiosum
D. Syphilis
E. Varicella-zoster

III-198. A 22-year-old woman presents with diffuse arthralgias and morning stiffness in her hands, knees, and wrists.

Two weeks earlier, she had a self-limited febrile illness notable for a red facial rash and lacy reticular rash on her extremities. On examination, her bilateral wrists, metacarpophalangeal joints, and proximal interphalangeal joints are warm and slightly boggy. Which of the following tests is most likely to reveal her diagnosis?

A. Antinuclear antibody
B. *Chlamydia trachomatis* ligase chain reaction of the urine
C. Joint aspiration for crystals and culture
D. Parvovirus B19 IgM
E. Rheumatoid factor

III-199. Which of the following statements regarding the currently licensed human papillomavirus (HPV) vaccines is true?

A. A single dose of the vaccine is effective in providing lifelong immunity.
B. All protect against genital warts.
C. The vaccines are recommended for males and females before starting primary school.
D. The vaccine has a therapeutic effect on active infection.
E. Women who have been vaccinated should continue to receive standard Pap smear testing.

III-200. A 32-year-old woman experiences an upper respiratory illness that began with rhinorrhea and nasal congestion. She also complains of a sore throat but has no fever. Her illness lasts for about 5 days and resolves. Just prior to her illness, her 4-year-old child who attends daycare also experienced a similar illness. All of the following statements regarding her illness are true EXCEPT:

A. The viruses can be implicated in lower respiratory tract disease.
B. The seasonal peak of the infection is in the winter in temperate climates.
C. The etiologic agent can be identified with reverse transcription-polymerase chain reaction testing.
D. The viruses causing this condition spread by small-particle aerosolization.
E. The most common cause of her condition is a single-stranded RNA virus of the Picornaviridae family.

III-201. All of the following respiratory viruses may cause a common cold syndrome in children or adults EXCEPT:

A. Adenoviruses
B. Coronaviruses
C. Enteroviruses
D. Human respiratory syncytial viruses
E. Rhinoviruses

III-202. All of the following viruses are correctly matched with their primary clinical manifestation EXCEPT:

A. Adenovirus: gingivostomatitis
B. Coronavirus: severe acute respiratory syndrome
C. Human respiratory syncytial virus: bronchiolitis in infants and young children
D. Parainfluenza: croup
E. Rhinovirus: common cold

III-203. A 22-year-old woman who has never received a vaccination returned from a trip to Israel 14 days ago. Four days ago she started to develop a cough, coryza, conjunctivitis, and fever to 40°C (104°F). Yesterday, she started to notice spots inside of her mouth. Today, she presents for a telemedicine appointment because of a diffuse rash affecting her face and trunk (Figure III-203). All of the following statements regarding this woman's infection are true EXCEPT:

A. Airborne transmission is common.
B. Her rash is considered diagnostic of the infection.
C. Severe infection can occur when primary infection occurs in an unvaccinated adult.
D. The infection has been eliminated in the United States.
E. Vaccination rates of >90% are required for herd immunity.

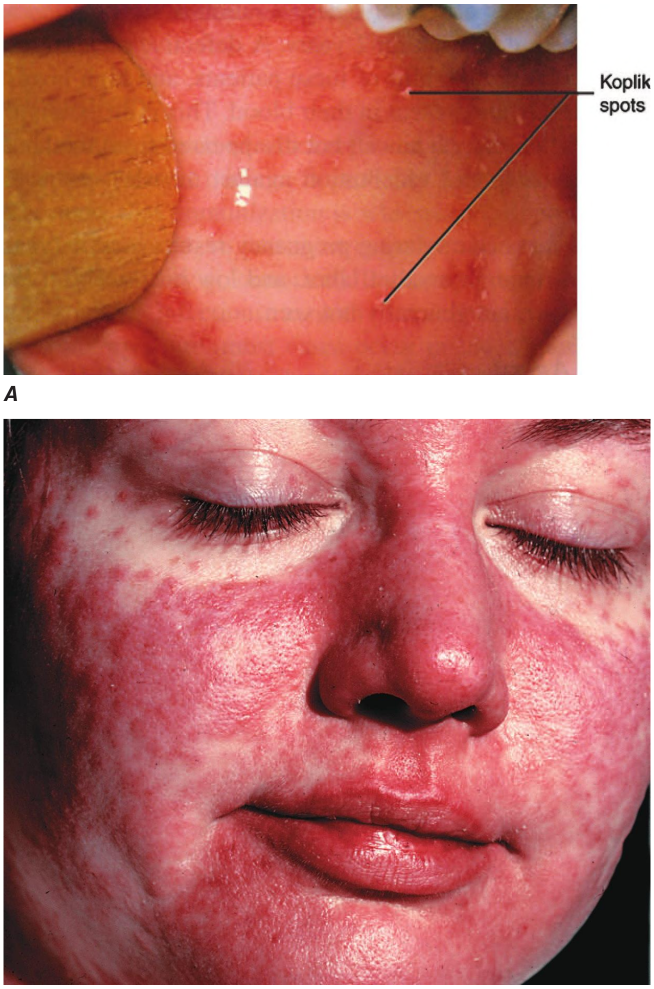


FIGURE III-203 ***(A)*** Reproduced with permission from Nester EW: *Microbiology: A Human Perspective*, 6th ed. New York: McGraw Hill, 2009. ***(B)*** Reproduced with permission from Wolff K et al: *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology*, 8th ed. New York: McGraw Hill, 2017.

III-204. A 52-year-old woman who was originally from northeastern Brazil presents with 2 years of right lower extremity weakness and low back pain. She is starting to experience urinary incontinence. She is noted to have hyperreflexia, ankle clonus, and extensor plantar responses on her right lower leg. An MRI is performed and shows lesions in the white matter and periventricular regions of the brain as well as the spinal cord. Her mother told her once that she was diagnosed with an "HIV-like virus." All of the following statements regarding the etiologic agent causing her syndrome are true EXCEPT:

A. The etiologic agent is a cause of adult T-cell leukemia.
B. The etiologic agent is also common in Okinawa.
C. The etiologic agent frequently results in disease.
D. The etiologic agent is often transmitted perinatally.
E. This condition impacts women more than men.

III-205. All of the following statements regarding HIV transmission are true EXCEPT:

A. Genital ulcerations increase the risk of HIV transmission.
B. HIV may be transmitted to infants in maternal breast milk.
C. HIV may be transmitted via a mosquito or tick bite.
D. The probability of acquiring HIV is greater during receptive anal intercourse than insertive anal intercourse.
E. The quantity of HIV in plasma is a primary determinant of the risk of HIV transmission.

III-206. A 36-year-old man with HIV/AIDS (CD4+ lymphocyte count = 54/μL) develops a red-purple nodular painless lesion on the tip of his nose. The rest of his skin examination is normal. Which of the following is the most likely diagnosis?

A. Molluscum contagiosum
B. Kaposi sarcoma
C. Psoriasis
D. Reactivation herpes zoster
E. Seborrheic dermatitis

III-207. Which of the following scenarios is most likely associated with the lowest risk of HIV transmission to a health care provider after an accidental needlestick from a patient with HIV?

A. The needle is visibly contaminated with the patient's blood.
B. The needlestick injury is a deep tissue injury to the health care provider.
C. The patient whose blood is on the contaminated needle has had successful viral suppression on current therapy.
D. The patient whose blood is on the contaminated needle was diagnosed with acute HIV infection 2 weeks ago.

III-208. All of the following are appropriate combinations of HIV antiretroviral agents with a major side effect EXCEPT:

A. Abacavir: severe hypersensitivity reaction
B. Dolutegravir: granulocytopenia
C. Stavudine: lipoatrophy
D. Tenofovir: Fanconi anemia
E. Zidovudine: macrocytic anemia

III-209. A 38-year-old man with HIV/AIDS presents with 4 weeks of diarrhea, fever, and weight loss. Which of the following tests established the diagnosis of cytomegalovirus (CMV) colitis?

A. CMV IgG
B. Colonoscopy with biopsy
C. Serum CMV polymerase chain reaction
D. Stool CMV antigen
E. Stool CMV culture

III-210. A 45-year-old man is admitted to the hospital with 2–3 weeks of fever, tender lymph nodes, and generalized abdominal pain. He reports progressive weight loss and malaise for over a year. On examination, he is found to be febrile and frail with temporal wasting and oral thrush. Matted, tender anterior cervical lymphadenopathy <1 cm are noted. He is diagnosed with AIDS (CD4+ lymphocyte count 30/μL and HIV RNA 650,000 copies/mL). Blood cultures grow *Mycobacterium avium*. He is started on rifabutin and azithromycin, as well as trimethoprim-sulfamethoxazole for Pneumocystis prophylaxis. He is then initiated on tenofovir disoproxil fumarate, emtricitabine, and dolutegravir. Two weeks later, he returns to the clinic with fevers, neck pain, and abdominal pain. His temperature is 39.2°C, heart rate is 110 beats/min, blood pressure is 110/64, and oxygen saturations are normal. His cervical nodes are now 2 cm in size and extremely tender, and one has fistulized to his skin and is draining yellow pus that is acid-fast bacillus stain positive. His hepatomegaly is pronounced and tender. Which of the following is the most likely explanation for his presentation?

A. HIV treatment failure
B. Immune reconstitution syndrome to *M. avium*
C. Kaposi sarcoma
D. *M. avium* treatment failure due to drug resistance
E. *Mycobacterium tuberculosis* infection

III-211. Current Centers for Disease Control and Prevention recommendations are that screening for HIV be performed in which of the following?

A. All high-risk groups (injection drug users, men who have sex with men, and high-risk heterosexual women)
B. All U.S. adults
C. Injection drug users
D. Men who have sex with men
E. Women who have sex with more than two men per year

III-212. A 38-year-old woman is seen in the clinic for a decrease in cognitive and executive function. Her husband is concerned because she is no longer able to pay bills, keep appointments, or remember important dates. She also seems to derive considerably less pleasure from caring for her children and participating in her hobbies. She is unable to concentrate for long enough to enjoy movies. This is a clear change from her functional status 6 months prior. A workup reveals a positive HIV antibody by enzyme immunoassay and Western blot. Her CD4+ lymphocyte count is 378/μL with a viral load of 78,000/mL. She is afebrile with normal vital signs. Her affect is blunted, and she seems disinterested in the medical interview. Neurologic examination for strength, sensation, cerebellar function, and cranial nerve function is nonfocal. Fundoscopic examination is normal. Mini-Mental Status Examination score is 22/30. A serum rapid plasmin reagin test is negative. MRI of the brain shows only cerebral atrophy disproportionate to her age but no focal lesions. Which of the following is the next step in her management?

A. Antiretroviral therapy
B. Cerebrospinal fluid (CSF) JC virus polymerase chain reaction (PCR)
C. CSF mycobacterial PCR
D. CSF VDRL test
E. Serum cryptococcal antigen

III-213. In an HIV-infected patient, *Cryptosporidium* infection is associated with which of the following?

A. Bloody diarrhea
B. Severe fulminant diarrheal syndrome
C. Pneumonia
D. Liver abscess
E. Arthritis

III-214. A 27-year-old man presents to your clinic with 2 weeks of sore throat, malaise, myalgias, night sweats, fevers, and chills. He visited an urgent care center and was told that he likely had the flu. He was told that he had a "negative test for mono." The patient has sex with men, states that he is in a monogamous relationship, and has unprotected receptive and insertive anal and oral intercourse with one partner. He had several partners prior to his current partner 4 years ago but none recently. He reports a negative HIV-1 test 2 years ago and recalls being diagnosed with *Chlamydia* infection 4 years ago. He is otherwise healthy with no medical problems. You wish to rule out the diagnosis of acute HIV. Which blood test should you order?

A. CD4+ lymphocyte count
B. HIV enzyme immunoassay/Western blot combination testing
C. HIV resistance panel
D. HIV RNA by polymerase chain reaction (PCR)
E. HIV RNA by ultrasensitive PCR

III-215. A 47-year-old woman with known HIV/AIDS (CD4+ lymphocyte = 106/μL and viral load = 35,000/mL) presents with painful growths on the side of her tongue as shown in Figure III-215A. Which of the following is the most likely diagnosis?

A. Aphthous ulcers
B. Hairy leukoplakia
C. Herpes stomatitis
D. Oral candidiasis
E. Oral Kaposi sarcoma

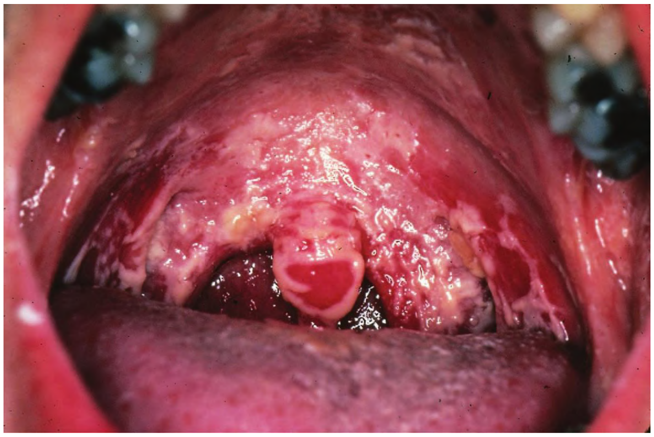

A

FIGURE III-215A

III-216. All of the following patients may be candidates to receive pre-exposure prophylaxis for HIV infection EXCEPT:

A. Sexually active adult men who have sex with men
B. Adult persons who inject drugs
C. Adult heterosexually active women who are at substantial risk of HIV acquisition.
D. Health care workers in an HIV clinic
E. Sexually active transgendered women who have sex with men

III-217. All of the following statements regarding antiretroviral therapy for HIV are true EXCEPT:

A. CD4+ lymphocyte count should rise by >100 within 2 months of initiation of therapy.
B. Intermittent administration regimens have equivalent efficacy to constant administration regimens.
C. Plasma HIV RNA should fall by 1 log order within 2 months of initiation of therapy
D. Viral genotype should be checked prior to initiation of therapy.

III-218. You are working as a physician on a cruise ship that has traveled to the eastern coast of Mexico. The cruise stopped in the Yucatan Peninsula yesterday. Since that stop, you have evaluated 54 people with nausea, vomiting, and watery diarrhea. Many patients have also complained of abdominal cramping and mild fever. All of the affected individuals disembarked yesterday but were not traveling together. They also have all eaten at the evening buffet on the ship. Physical examination of affected individuals generally shows no abdominal tenderness. A few patients have required IV rehydration. Which of the following organisms do you suspect as the cause of the outbreak?

A. *Bacillus cereus*
B. Enterotoxigenic *Escherichia coli*
C. Group A rotavirus
D. *Norovirus*
E. *Staphylococcus aureus*

III-219. You are working as a public health practitioner in a county of 100,000 individuals. You are asked to investigate an outbreak of a febrile illness accompanied by rash at a small, private preschool. The initial case of illness occurred in a 28-year-old teacher who had recently returned from visiting her family in Ukraine. She received her usual childhood immunizations at that time. Her illness began with fever and fatigue about 14 days ago. She stayed home from work until the fever subsided 6 days ago. Subsequently, she had onset of a rash that is erythematous and macular. It began on the face, neck, and near the hairline but has become generalized and confluent on the trunk. When examining her oral mucosa, the lesion shown in Figure III-219 is seen. There are now four children in the preschool exhibiting a high fever, and two have developed a similar rash. Review of medical records at this school shows nonvaccination rates of 25%. Which of the following vaccine-preventable illnesses is most likely?

A. Measles
B. Mumps
C. Poliovirus
D. Rubella
E. Varicella

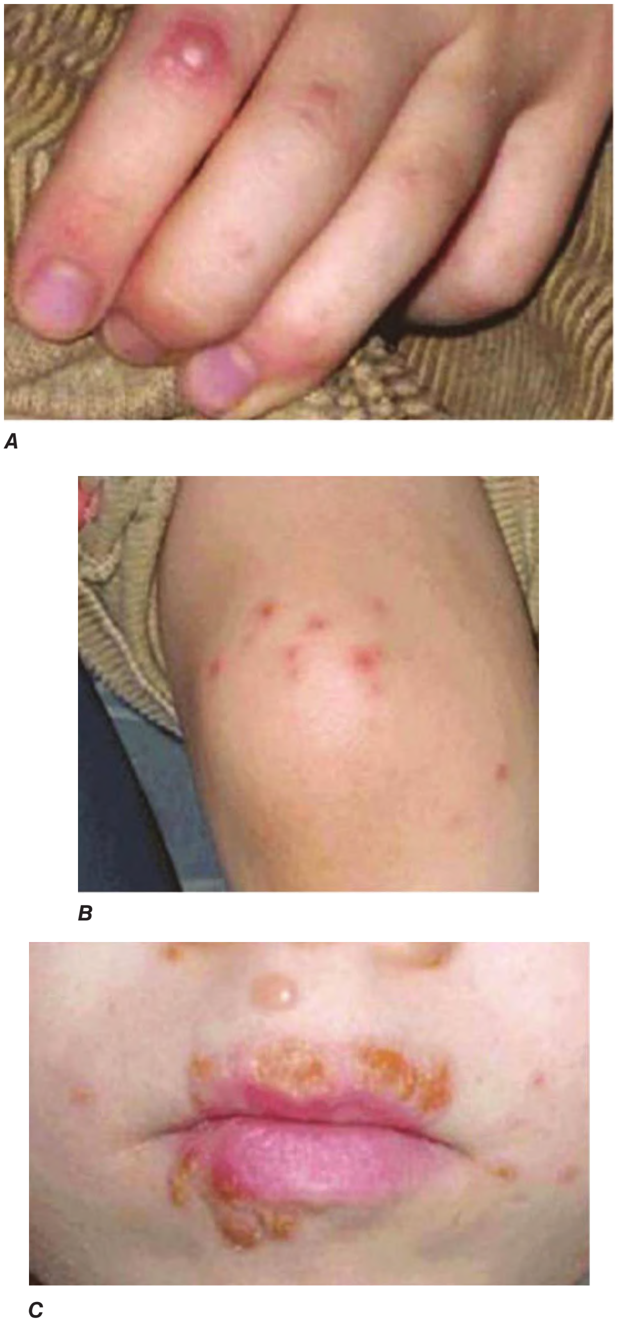


FIGURE III-219 Reproduced with permission from Centers for Disease Control and Prevention.

III-220. You are treating a 5-year-old child who was not vaccinated for measles. The child was exposed at a playground where an individual who had the disease was present. The child is having fevers of 39°C (102.1°F), has a diffuse erythematous macular rash, and has Koplik spots. Which of the following treatments do you recommend at this time?

A. IVIg
B. Prophylactic antibacterial therapy with a penicillin or cephalosporin to prevent pneumonia
C. Ribavirin
D. Supportive care only
E. Vitamin A

III-221. A 17-year-old young woman who has never received a vaccination is 10-weeks pregnant with her first child. She has not yet received any prenatal care. She presents with 5 days of low-grade fevers, malaise, rhinitis, and cough and two days of a generalized maculopapular rash (Figure III-221). In addition, she has generalized arthritis and arthralgias. As a result of this illness, her child is at risk of all of the following conditions, EXCEPT:

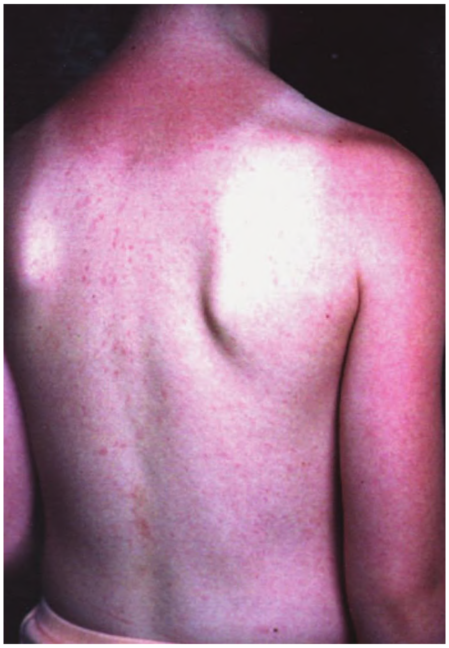


FIGURE III-221

A. Abnormal notched or peg-shaped teeth ("Hutchinson teeth")
B. Autism
C. Hearing impairment/deafness
D. Patent ductus arteriosus
E. Thrombocytopenia with purpura/petechiae ("blueberry muffin syndrome")

III-222. A 19-year-old male college student presents to student health with 4 days of bilateral tender, self-limited swelling of the parotid gland (Figure III-222). Prior to this, he had low-grade fevers, malaise, myalgias, headaches, and anorexia. In addition, he has noted tender orchitis. As a child, his family moved often so he does not recall his vaccination history. Several others at his college have presented with similar symptoms. What should he be told about the course of his illness?

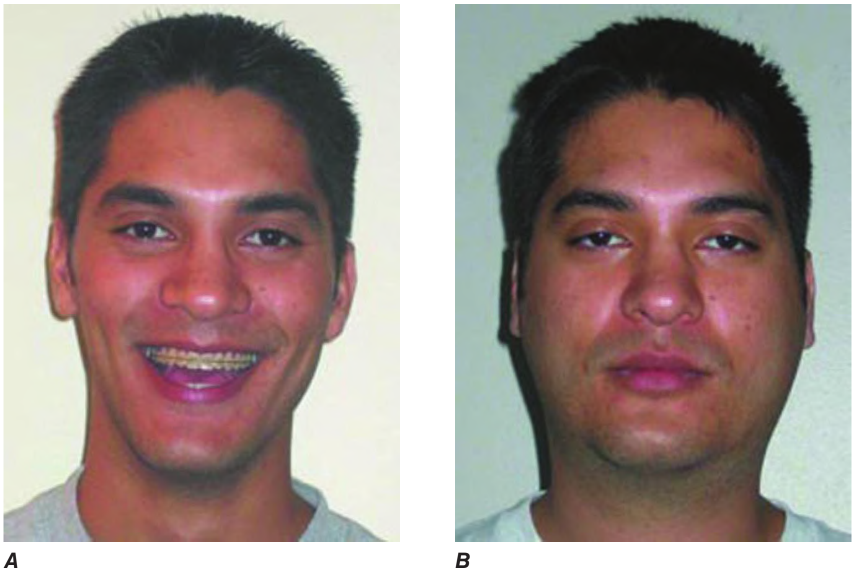


FIGURE III-222 Reproduced with permission from Shanley JD: The resurgence of mumps in young adults and adolescents. *Cleve Clin J Med* 74:42, 2007.

A. Meningitis is unlikely.
B. Parotitis will likely subsist for months.
C. Sterility is common.
D. Subfertility may occur in 30–87% of cases.
E. Vaccination is lifelong.

III-223. A 23-year-old previously healthy female letter carrier works in a suburb in which the presence of rabid foxes and skunks has been documented. She is bitten by a bat, which then flies away. Initial examination reveals a clean break in the skin in the right upper forearm. She is unsure about vaccination against rabies or tetanus. Which of the following is the next best step in her management?

A. Clean the wound with a 20% soap solution
B. Clean the wound with a 20% soap solution and administer tetanus toxoid
C. Clean the wound with a 20% soap solution, administer tetanus toxoid, and administer human rabies immune globulin IM
D. Clean the wound with a 20% soap solution, administer tetanus toxoid, administer human rabies immune globulin IM, and administer human diploid cell rabies vaccine
E. Clean the wound with a 20% soap solution and administer human diploid cell rabies vaccine

III-224. While working in Kuala Lumpur, Malaysia, a 40-year-old previously healthy male from Baltimore develops sudden-onset malaise, fever, headache, retro-orbital pain, backache, and myalgias. On examination, his temperature is 39.6°C with normal blood pressure and slight tachycardia. He has some vesicular lesions on his palate and scleral injection. Laboratory studies are notable for a platelet count of 80,000/μL. All of the following are true regarding his illness EXCEPT:

A. A second infection could result in hemorrhagic fever.
B. After resolution, he has lifelong immunity.
C. IgM enzyme-linked immunosorbent assay may be diagnostic.
D. In equatorial areas, year-round transmission occurs.
E. The disease is transmitted by mosquitoes.

III-225. Which of the following statements regarding chikungunya virus disease is true?

A. Baloxavir can be used as treatment.
B. It is common in Argentina.
C. It can be found in the Caribbean.
D. Severe arthralgias are common and can last for years.
E. Rashes can last for months.

III-226. All of the following are associated with Zika virus infection except which of the following?

A. Fetal microcephaly
B. Guillain-Barré
C. Itchy maculopapular rash
D. Petechiae
E. Vomiting

III-227. All of the following statements regarding Ebola virus disease (EVD) are true EXCEPT:

A. Abdominal pain and diarrhea are common manifestations of EVD.
B. EVD is frequently spread human-to-human via respiratory aerosols.
C. Patients who survive EVD often have severe sequelae such as arthralgias and asthenia.
D. There are no effective antimicrobials for EVD.
E. Viruses of the Filoviridae family cause EVD.

III-228. A 43-year-old woman with a history of rheumatoid arthritis is admitted to the hospital with respiratory failure. She was started on infliximab 2 months ago due to refractory disease. Prior to initiation of the medication, her physician found no evidence of latent tuberculosis infection. She reports 2 days of fever and worsening shortness of breath. On admission, she is hypotensive and hypoxemic with a chest radiograph showing bilateral interstitial and reticulonodular infiltrates. After administration of fluids and broad-spectrum antibiotics, intubation, and initiation of mechanical ventilation, a bronchoalveolar lavage (BAL) is performed. A silver stain of the BAL fluid shows the organisms shown in Figure III-228. Which of the following is the most likely causative organism?

A. *Aspergillus fumigatus*
B. Cytomegalovirus
C. *Histoplasma capsulatum*
D. *Blastomyces dermatitidis*
E. *Mycobacterium tuberculosis*

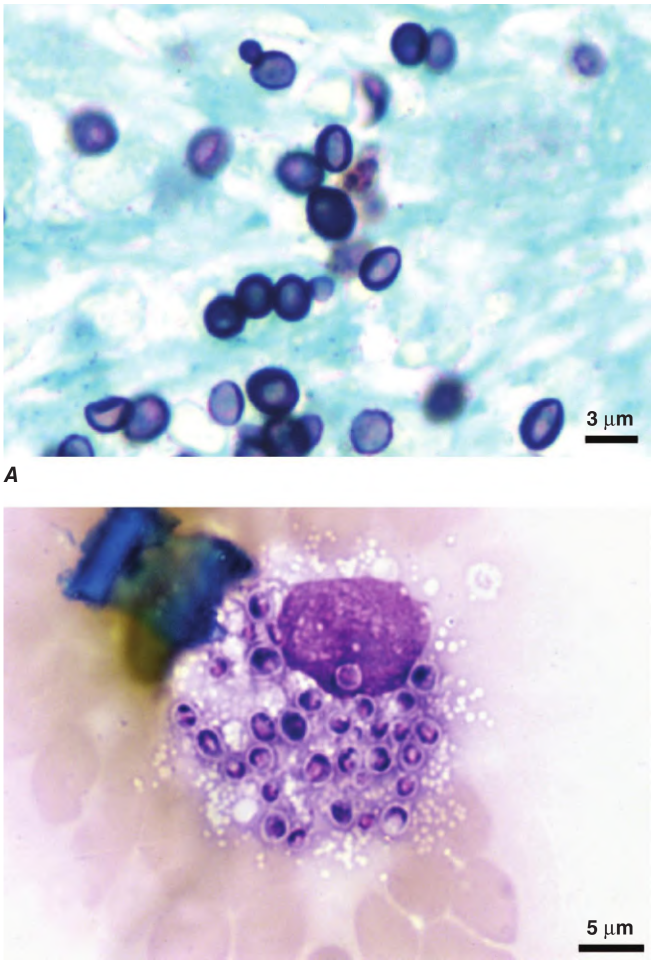


FIGURE III-228

III-229. In the patient described in question III-228, which of the following therapies should be initiated?

A. Caspofungin
B. Fluconazole
C. Ganciclovir
D. Isoniazid/rifampin/pyrazinamide/ethambutol
E. Liposomal amphotericin B

III-230. A 30-year-old man originally from the Philippines presents with a week of severe headache, fever, worsening mental status, confusion, and lethargy. He works as an architect in Sacramento, California, and has recently been visiting construction sites throughout the region. He has a history of Crohn disease for which he is on infliximab. On examination, he appears confused. His vital signs include blood pressure of 105/55, heart rate of 110 beat/min, respiratory rate of 20 breaths/min, oxygen saturation of 95% on room air, and temperature of 38.5°C. He has mild nuchal rigidity and significant photophobia. Lumbar puncture shows 450 white blood cells (80% lymphocytes), glucose of 20 mg/dL, and protein of 150 mg/dL. A silver stain of the cerebrospinal fluid is performed and shows large, round structures with thick walls containing small round spores and internal septations. Which of the following should you use for initial therapy?

A. Micafungin
B. Ceftriaxone
C. Penicillin G
D. Amphotericin
E. High-dose fluconazole

III-231. You are a physician for an undergraduate university health clinic in Arizona. You have evaluated three students with similar complaints of fever, malaise, diffuse arthralgias, cough without hemoptysis, and chest discomfort, and one of the patients has a skin rash on her upper neck consistent with erythema multiforme. Chest radiography is similar in all three, with hilar adenopathy and small pleural effusions. Her complete blood count is notable for eosinophilia. On further questioning, you learn that all three students are in the same archaeology class and participated in a local excavation 1 week ago. What is your leading diagnosis?

A. Mononucleosis
B. *Legionella* pneumonia
C. Primary pulmonary coccidioidomycosis
D. Primary pulmonary histoplasmosis
E. Streptococcal pneumonia

III-232. A 62-year-old man returns from a vacation to Arizona with fever, pleurisy, and a nonproductive cough. All of the following factors on history and laboratory examination favor a diagnosis of pulmonary coccidioidomycosis rather than community-acquired pneumonia EXCEPT:

A. Eosinophilia
B. Erythema nodosum
C. Mediastinal lymphadenopathy on chest x-ray
D. Positive *Coccidioides* complement fixation titer
E. Travel limited to the Grand Canyon

III-233. All of the following factors are commonly associated with a diagnosis of blastomycosis EXCEPT:

A. Alveolar infiltrates with consolidation
B. Laryngeal lesions
C. Osteomyelitis
D. Residing in southern Arizona
E. Skin lesions that can be mistaken for squamous cell carcinoma

III-234. A 43-year-old man comes to the physician complaining of 1 month of low-grade fever, malaise, shortness of breath, and a growing skin lesion. He resides in the upper peninsula of Michigan and works as a landscaper. He avoids medical care as much as possible. He is on no medications and smokes 2 packs per day of cigarettes. Over the last month, he notices that his daily productive cough has worsened, and the phlegm is dark yellow. He also reports that he has developed a number of skin lesions that start as painful nodules then, over a week, ulcerate and discharge pus (Figure III-234). His physical examination is notable for egophony and bronchial breath sounds in the right lower lobe, and approximately 5–10 ulcerating 4- to 8-cm skin lesions on the lower extremities consistent with the one shown in Figure III-234. His chest radiograph shows right lower lobe consolidation with no pleural effusion and no evidence of hilar or mediastinal adenopathy. After obtaining sputum for cytology and culture and a biopsy of the skin lesion, which is the next most likely diagnostic or therapeutic intervention?

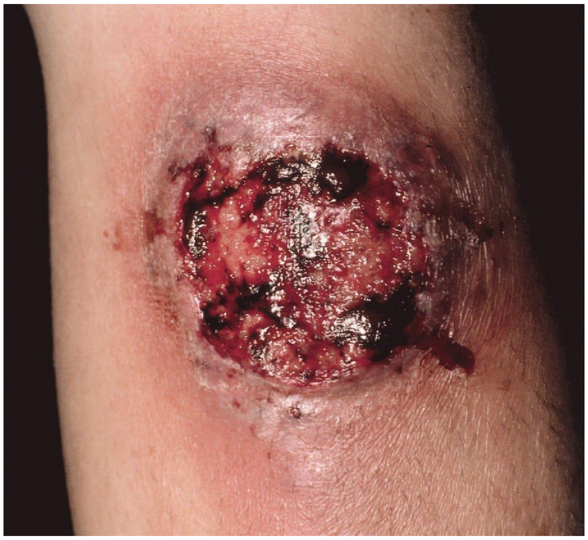


FIGURE III-234 Reproduced with permission from Kang S et al: *Fitzpatrick's Dermatology*, 9th ed. New York: McGraw Hill, 2019. Photo contributor: Elizabeth M. Spiers, MD.

A. Colonoscopy to evaluate for inflammatory bowel disease
B. Isoniazid/rifampin/pyrazinamide/ethambutol
C. Itraconazole
D. Positron emission tomography scan to evaluate for metastatic malignant disease
E. Vancomycin

III-235. A 34-year-old female aviary worker who has no significant past medical history, is taking no medications, has no allergies, and is HIV-negative presents to the emergency department with fever, headache, and fatigue. She reports that her headache has been present for at least 2 weeks, is bilateral, and is worsened by bright lights and loud noises. She is typically an active person who has recently been fatigued and has lost 8 lb due to anorexia. Her work involves caring for parakeets in a pet store and maintaining their habitat. Her vital signs are notable for a temperature of 39°C. Neurologic examination is normal except for notable photophobia. Head CT examination is normal. Lumbar puncture is significant for an opening pressure of 20 cm H_2O, white blood cell count of 15 cells/μL (90% monocytes), protein of 0.5 g/L (50 mg/mL), glucose of 2.8 mmol/L (50 mg/dL), and positive India ink stain. What is the appropriate therapy for this patient?

A. Amphotericin B for 2 weeks followed by lifelong fluconazole
B. Amphotericin B plus flucytosine for 2 weeks followed by oral fluconazole for 10 weeks
C. Caspofungin for 3 months
D. Ceftriaxone and vancomycin for 2 weeks
E. Voriconazole for 3 months

III-236. An HIV-positive patient with a CD4 count of 54 cells/μL who is not taking any medications presents to an urgent care center with complaints of a headache for the past week. He also notes nausea and blurred vision. Examination is notable for normal vital signs without fever but mild papilledema. Head CT does not show dilated ventricles. What is the most sensitive diagnostic test for this patient?

A. Cerebrospinal fluid (CSF) for cryptococcal antigen
B. CSF for India Ink stain
C. MRI with gadolinium imaging
D. Ophthalmologic examination including visual field testing
E. Pulmonary CT

III-237. Which of the following is a risk factor for hematogenously disseminated candidiasis?

A. Broad-spectrum antibacterial agents
B. Pulmonary alveolar proteinosis
C. Renal dysfunction
D. Sarcoidosis
E. Tumor necrosis factor-α inhibitor use

III-238. A 19-year-old man is undergoing intensive chemotherapy for acute myelogenous leukemia. He has been neutropenic for >5 days and is on prophylactic meropenem and vancomycin for 3 days in addition to parenteral alimentation. His absolute neutrophil count yesterday was 50, and today, it is 200. He had a fever spike to 38.3°C (101°F) yesterday. A chest/abdomen CT at that time was unremarkable. You are asked to see him because over the last 3 hours he has developed fever >38.8°C (102°F), severe myalgias and joint pains, and new skin lesions (Figure III-238). New skin lesions are appearing in all body areas. Initially they are red areas that become macronodular and are mildly painful. Vital signs are otherwise notable for a blood pressure of 100/60 and heart rate of 105 beats/min. An urgent biopsy of the skin lesion is most likely to show which of the following?

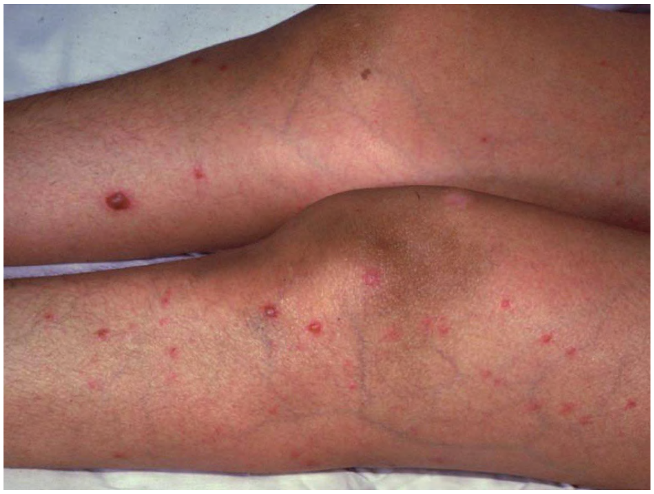


FIGURE III-238 Used with permission from Dr. Noah Craft and the Victor Newcomer collection at UCLA, archived by Logical Images, Inc.

A. Branching (45°) septated hyphae on methenamine silver stain
B. Budding yeast on methenamine silver stain
C. Encapsulated yeast on India ink stain
D. Pseudohyphae and hyphae on tissue Gram stain
E. Rounded internally septated spherules on methenamine silver stain

III-239. In the patient described in question III-238, all of the following medications are appropriate additions to the current antibiotic regimen EXCEPT:

A. Amphotericin
B. Micafungin
C. Fluconazole
D. Flucytosine
E. Voriconazole

III-240. In which of the following situations should you use antifungal agents to prevent *Candida* infections?

A. Allogeneic stem cell transplant recipients
B. Prophylaxis against oropharyngeal candidiasis in patients infected with HIV and CD4+ T-cell lymphocyte counts <200cells/μL
C. Widespread prophylaxis in medical intensive care unit patients against invasive candidiasis
D. Widespread prophylaxis in surgical intensive care unit patients against invasive candidiasis
E. Women on broad-spectrum antibiotics to prevent vaginal candidiasis

III-241. A 72-year-old man is admitted to the hospital with bacteremia and pyelonephritis. He is HIV negative and has no other significant past medical history. Two weeks into his treatment with antibiotics through a central venous catheter, a fever evaluation reveals a blood culture positive for *Candida albicans*. Examination is unremarkable. White blood cell count is normal. The central venous catheter is removed, and systemic antifungal agents are initiated. What further evaluation is recommended?

A. Abdominal CT scan to evaluate for abscess
B. Chest x-ray
C. Funduscopic examination
D. Lumbar puncture with cerebrospinal fluid fungal cultures
E. MRI lumbar spine

III-242. An inpatient bone marrow transplant unit has recently had frequent outbreaks of invasive *Aspergillus*. Which of the following is the most likely source?

A. Highway construction project right next to the hospital
B. Overuse of central venous catheters
C. Poor adherence to masking protocols
D. Poor hand hygiene among staff
E. Poor sanitation in the in-room sinks

III-243. A 23-year-old man receiving chemotherapy for relapsed acute myelogenous leukemia has had persistent neutropenia for the past 4 weeks. Over the past 5 days, his absolute neutrophil count has risen from 0 to 200, and he has had persistent fevers despite receiving cefepime/vancomycin empiric therapy. Other than fever, tachycardia, and malaise, he has no focal findings and his vital signs are otherwise unremarkable, including a normal oxygen saturation on room air. A chest/abdomen CT performed due to the fever shows a few scattered 1- to 2-cm nodules with surrounding ground-glass infiltrates in the lower lobes.

Which of the following tests will most likely be positive in this patient?

A. Serum cryptococcal antigen
B. Serum galactomannan assay
C. Sputum fungal culture
D. Urine *Histoplasma* antigen
E. Urine *Legionella* antigen

III-244. In the patient described in question III-243, which of the following medications should be initiated immediately?

A. Amphotericin B
B. Caspofungin
C. Fluconazole
D. Trimethoprim-sulfamethoxazole
E. Voriconazole

III-245. A 36-year-old woman with a past medical history of poorly controlled asthma presents with a chronic cough refractory to treatment of her asthma. She has been diagnosed with pneumonia multiple times. She often has intermittent wheezing and thick brownish sputum. She has coughed up thick sputum casts multiple times. As her primary care doctor, you order a chest CT, which shows bronchiectasis and hyperattenuated mucus in the airways. In addition, her allergist orders a serum IgE, which is highly elevated at 1500 IU/mL, and an eosinophil level, which is elevated at 800 cells/μL. Which of the following is the most important diagnostic test in this patient?

A. Serum *Aspergillus*-specific IgE
B. Sputum bacterial culture
C. Sputum culture for mycobacteria
D. Sputum methenamine silver stain
E. Urine histoplasmosis antigen

III-246. A 56-year-old man with a history of untreated pulmonary sarcoidosis with multiple bullae presents with 3 months of cough productive of purulent sputum, fatigue, weight loss, and low-grade fevers. He has had negative screening tests for tuberculosis. Sputum cultures for acid-fast bacillus are overgrown with a hyaline, septate, and branching mold. His CT is shown in Figure III-246. What medical treatments should be initiated?

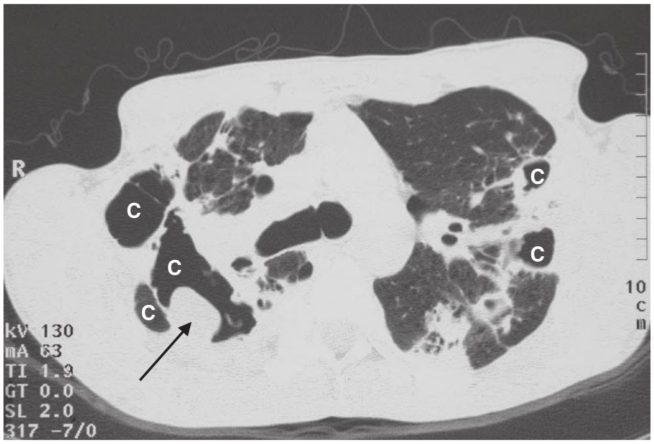


FIGURE III-246

A. Azithromycin/rifampin
B. Fluconazole
C. Itraconazole
D. Rifampin/isoniazid/pyrazinamide/ethambutol
E. Trimethoprim/sulfamethoxazole

III-247. Patients with all of the following conditions have increased risk of developing mucormycosis EXCEPT:

A. Deferoxamine therapy
B. Factitious hypoglycemia
C. Glucocorticoid therapy
D. Metabolic acidosis
E. Neutropenia

III-248. A 38-year-old woman with a history of diabetes mellitus, hypertension, and chronic renal insufficiency comes to the emergency department complaining of double vision for 1 day. She has required chronic hemodialysis for 8 years and often misses appointments, including four of her last eight sessions. She also notes 12 hours of facial swelling and difficulty speaking. She appears to be in moderate distress. Her vital signs are notable for a temperature of 39.0°C, blood pressure of 155/95, heart rate of 110 beats/min, and respiratory rate of 25 breaths/min. Her head examination demonstrates right-sided proptosis, facial edema, and a facial palsy (Figure III-248). Laboratory examination reveals a white blood cell count of 15,000/μL, serum glucose of 225 mg/dL, serum creatinine of 6.3 mg/dL, and hemoglobin A1c of 9.7%. Arterial blood gas on room air is as follows: pH 7.24, PCO_2 20 mmHg, and PO_2 100 mmHg. She is immediately brought to the intensive care unit, and a needle aspirate of a retro-orbital mass is performed. On-site cytopathology reveals wide, thick-walled, ribbon-shaped, nonseptate hyphal organisms that branch at 90 degrees. All of the following are components of the initial therapy for her likely infection EXCEPT:

A. Hemodialysis
B. Insulin
C. Liposomal amphotericin B
D. Surgical debridement
E. Voriconazole

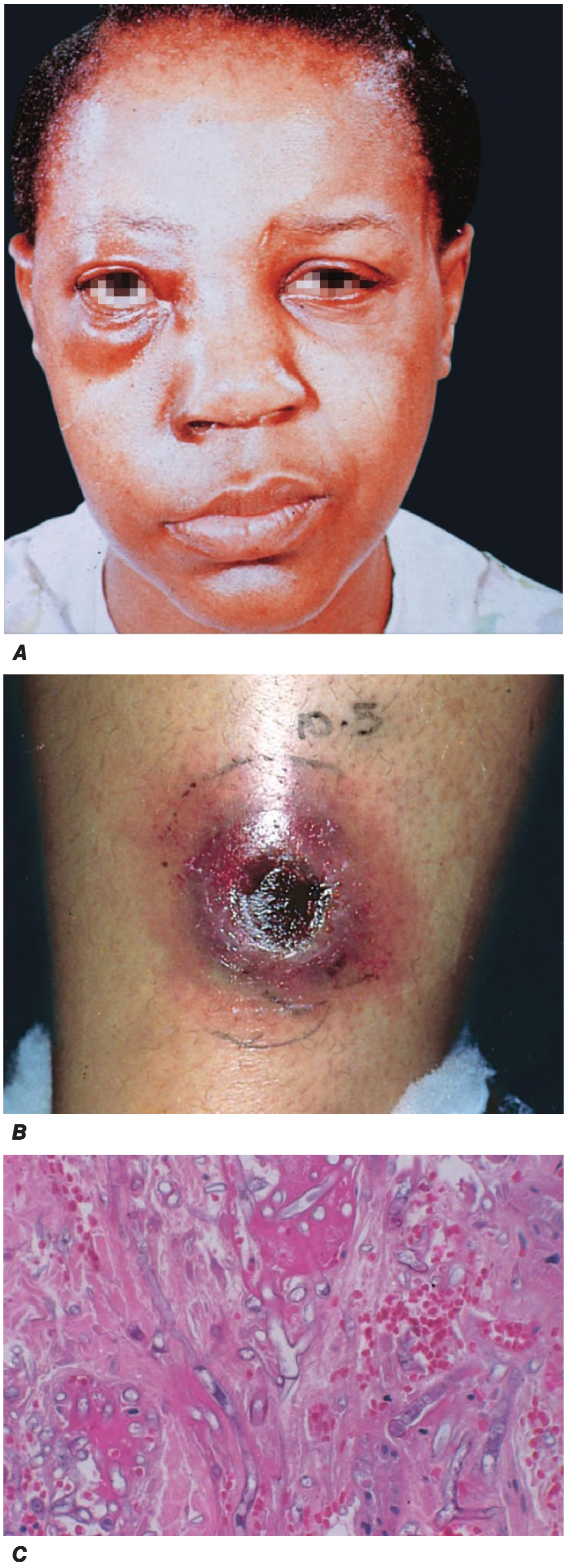


FIGURE III-248 Reproduced with permission from Kang S et al: *Fitzpatrick's Dermatology*, 9th ed. New York: McGraw Hill, 2019.

III-249. A 21-year-old college student seeks your opinion because of a lesion on his head. He has no significant medical history and reports a solitary lesion on the crown of his head for over 1 month that has been growing slowly. He has had no fever and reports that while the area is itchy he feels well. On examination, you note a 3-cm round area of alopecia without redness, pain, or inflammation. It is well demarcated with central clearing, scaling, and broken hair shafts at the edges. There is no redness or pain. Which of the following should you recommend?

A. Caspofungin
B. Clindamycin
C. Doxycycline
D. Minoxidil
E. Terbinafine

III-250. A 34-year-old man seeks the advice of his primary care physician because of an asymptomatic rash on his chest. There are coalescing light brown to salmon-colored macules present on the chest. A scraping of the lesions is viewed after a wet preparation with 10% potassium hydroxide solution. There are both hyphal and spore forms present, giving the slide an appearance of "spaghetti and meatballs." In addition, the lesions fluoresce to a yellow-green appearance under a Wood lamp. Tinea versicolor is diagnosed. Which of the following microorganisms is responsible for this skin infection?

A. *Fusarium solani*
B. *Malassezia furfur*
C. *Penicillium marneffei*
D. *Sporothrix schenckii*
E. *Trichophyton rubrum*

III-251. A 45-year-old woman with no past medical history presents in July with 3 weeks of a rash on her hand

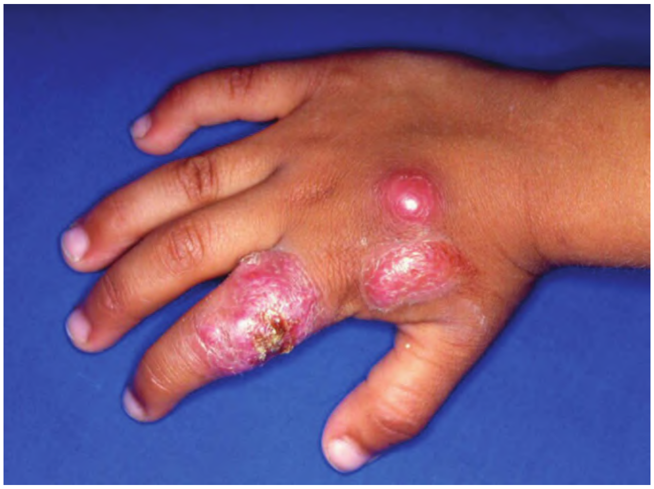


FIGURE III-251 Used with permission from Dr. Angela Restrepo.

(Figure III-251). It is not painful. She has noticed spread of the rash up her arm. She is an avid gardener and enjoys cultivating roses, but also lives by a river and enjoys swimming in the river. A biopsy is performed and shows a mixed granulomatous and pyogenic reaction. Tiny oval yeasts can be seen. Which of the following is the most appropriate treatment of her condition?

A. Clarithromycin and ethambutol
B. Fluconazole
C. Itraconazole
D. Trimethoprim-sulfamethoxazole
E. Voriconazole

III-252. A 35-year-old woman with long-standing rheumatoid arthritis has been treated with infliximab for the last 6 months with improvement of her joint disease. She has a history of positive purified protein derivative and takes isoniazid prophylaxis. For the past week, she reports worsening dyspnea on exertion with low-grade fevers and a nonproductive cough. On examination, her vital signs are notable for normal blood pressure, temperature of 38.0°C, heart rate of 105 beats/min, respiratory rate of 22 breaths/min, and SaO_2 of 91% on room air. Her lungs are clear. Within one flight of steps, she becomes dyspneic and her SaO_2 falls to 80%. A representative image from her chest CT scan is shown in Figure III-252. Which of the following is the most likely diagnosis?

A. *Aspergillus fumigatus* pneumonia
B. *Nocardia asteroides* pneumonia
C. *Pneumocystis jiroveci* pneumonia
D. Rheumatoid nodules
E. Staphylococcal bacteremia and septic pulmonary emboli

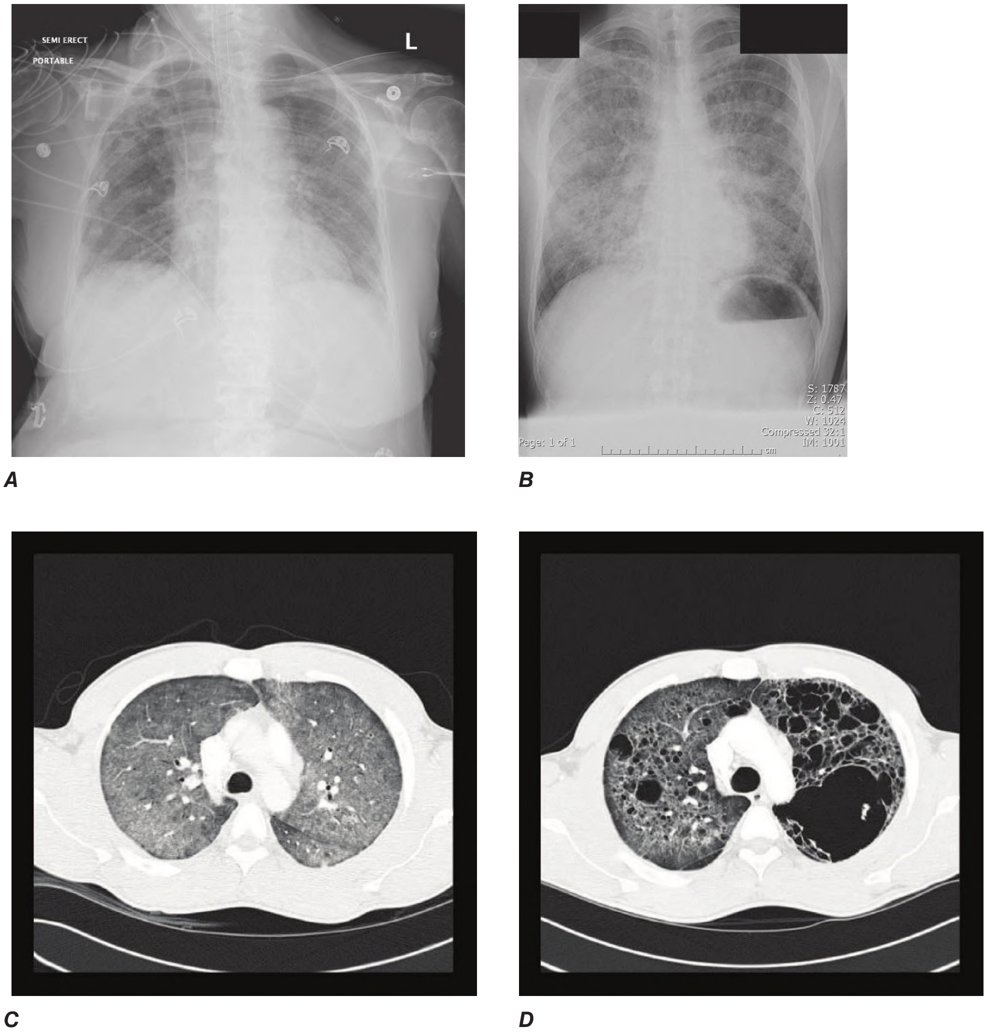


FIGURE III-252

III-253. Which of the following patients should receive prophylaxis against *Pneumocystis jiroveci* pneumonia?

A. A patient newly diagnosed with HIV who has a CD4+ T-cell count of 152/μL
B. A patient placed on 5 days of prednisone 60 mg daily for an asthma exacerbation
C. A patient with HIV on chronic treatment whose CD4+ T-cell count is currently 415/μL and was 565/μL 3 months ago
D. A patient with ulcerative colitis who has been on prednisone 10 mg daily for the last 6 weeks

III-254. A 45-year-old woman with known HIV infection and medical nonadherence to therapy is admitted to the hospital with 2–3 weeks of increasing dyspnea on exertion and malaise. Chest radiograph shows bilateral alveolar infiltrates, and induced sputum is positive for *Pneumocystis jiroveci*. Her PaO_2 on room air is 61 mmHg with an oxygen saturation of 88%. Which of the following is the best treatment option for her?

A. Trimethoprim-sulfamethoxazole
B. Trimethoprim-sulfamethoxazole and prednisone 60 mg PO daily
C. IV pentamidine
D. Oral clindamycin and IV primaquine
E. Dapsone

III-255. A 35-year-old migrant fruit picker originally from El Salvador is evaluated for right upper quadrant pain, fever, and hepatic tenderness. He reports no diarrhea or bloody stool. A representative image from his abdominal CT scan is shown in Figure III-255. Of note, he has been in the United States for approximately 10 years and was well until approximately 10 days ago. Which of the following tests can be used to confirm the diagnosis?

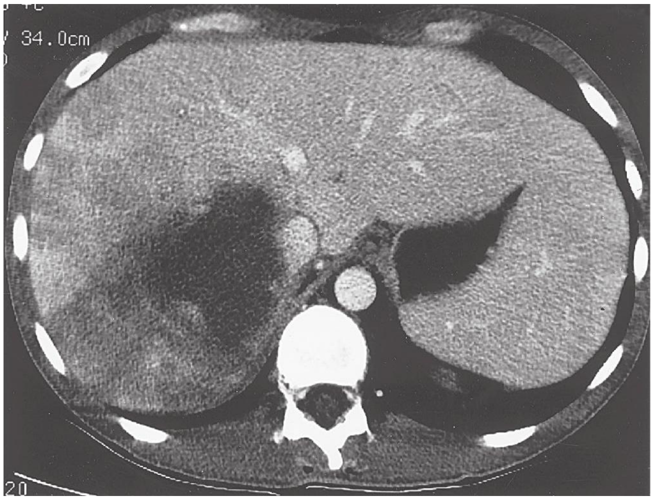


FIGURE III-255 Used with permission from Department of Radiology, UCSD Medical Center, San Diego.

A. Examination of stool for trophozoites
B. Liver biopsy
C. Polymerase chain reaction of stool for *Campylobacter*
D. Response to empiric trial of iodoquinol
E. Serologic test for antibody to *Entamoeba histolytica*

III-256. A 22-year-old woman who left her home in Nigeria 2 nights ago started to develop fevers while on the plane. On landing, her family was concerned due to her deteriorating mental status. She is now confused and lethargic. Her physical examination is notable for a temperature of 40°C, heart rate of 145 beats/min, and systemic blood pressure of 105/62. A thin smear for malaria is performed (Figure III-256). How should you treat her?

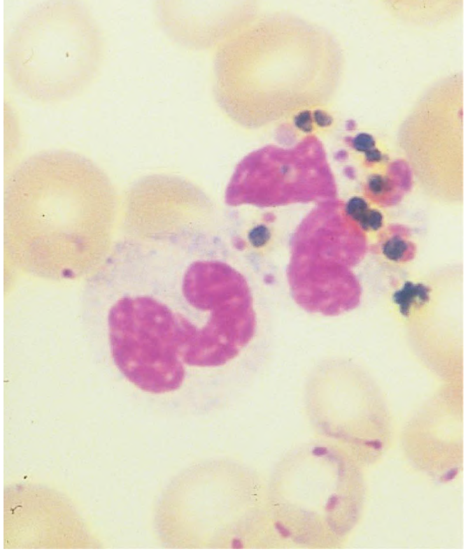


FIGURE III-256 Reproduced with permission from *Bench Aids for the Diagnosis of Malaria Infections*, 2nd ed. World Health Organization.

A. IM artemether
B. IV artesunate
C. IV quinidine
D. IV quinine
E. Oral mefloquine

III-257. A 28-year-old woman presents with fevers, headache, diaphoresis, and abdominal pain 2 days after returning from an aid mission to the coast of Papua New Guinea. Several of her fellow aid workers developed malaria while abroad, and she stopped her doxycycline prophylaxis due to a photosensitivity reaction 5 days prior. You send blood cultures, routine labs, and a thick and thin smear to evaluate the source of her fevers. Which of the following statements is accurate in reference to diagnosis of malaria?

A. A thick smear is performed to increase sensitivity compared with a thin smear but has a longer processing time.
B. Careful analysis of the thin blood film allows for prognostication based on estimation of parasitemia and morphology of the erythrocytes.
C. In the absence of rapid diagnostic information, empirical treatment for malaria should be strongly considered.
D. Morphology on blood smear is the current criterion used to differentiate the four major species of Plasmodium that infect humans.
E. All of the above are true.

III-258. A 23-year-old man with a past medical history of well-controlled HIV (CD4+ T-cell lymphocyte count 655 cells/μL) and depression is spending a rotation in veterinary school in a game park in Kenya. He has a history of G6PD deficiency. Which of the following should you prescribe for malaria prophylaxis?

A. Mefloquine starting 2 days prior to travel through 2 week after travel
B. Doxycycline starting 2 days prior to travel through 2 weeks after travel
C. Atovaquone-proguanil starting 2 days prior to travel through 1 week after travel
D. Primaquine starting 2 days prior to travel through 2 weeks after travel
E. Chloroquine starting 1 week prior to travel through 4 weeks after travel

III-259. A 54-year-old man recently returned from a month-long vacation on Nantucket Island in Massachusetts during August. Two weeks after his return, he develops the gradual onset of fever that has reached as high as 40°C, fatigue, malaise, and weakness. With the fever he has had chills, sweats, headache, myalgia, and anorexia. On examination, he is febrile with normal vital signs and has mild hepatomegaly and splenomegaly. A complete blood count is obtained and shows a hemoglobin of 10g/dL, a platelet count of 100,000/μL, and a neutrophil count of 1000/μL. His alkaline phosphatase, alanine and aspartate aminotransferases, and bilirubin levels are all elevated. Which of the following tests should be performed?

A. Coxsackie A virus antibody
B. Enzyme-linked immunosorbent assay test for *Borrelia burgdorferi*
C. Giemsa-stained thin blood smear
D. Rapid plasma reagin
E. Rapid influenza antigen test

III-260. A 35-year-old man from India is seen for evaluation of several weeks of fever that has decreased in intensity, but he now has developed abdominal swelling. He has no significant past medical history. Physical examination shows palpable splenomegaly and hepatomegaly and diffuse lymphadenopathy. Diffuse hyperpigmentation is present in his skin. Visceral leishmaniasis is suspected. Which of the following diagnostic techniques is most commonly employed?

A. Culture of peripheral blood for *Leishmania*
B. Polymerase chain reaction for *Leishmania infantum* nucleic acid in peripheral blood
C. Rapid immunochromatographic test for recombinant antigen rK39 from *L. infantum*
D. Smear of stool for amastigotes
E. Splenic aspiration to demonstrate amastigotes

III-261. All of the following statements regarding infection with *Trypanosoma cruzi* are true EXCEPT:

A. It is transmitted to humans by the bite of deer ticks.
B. It may be transmitted by blood transfusion.
C. It may cause acute and chronic disease.
D. It often leads to cardiac complications.
E. It should be suspected in patients returning from South America.

III-262. A 36-year-old man is admitted to the hospital with 3 months of worsening dyspnea on exertion and orthopnea. Over the last 2 weeks he has been sleeping upright. He denies any chest pain with exertion or syncope. There is no history of hypertension, hyperlipidemia, or diabetes. He is a lifelong nonsmoker and, since arriving to the United States from rural Peru 16 years ago, works as an electrician. His physical examination is notable for being afebrile with a heart rate of 105 beats/min, blood pressure of 100/80, respiratory rate of 22 breaths/min, and oxygen saturation of 88% on room air. He has notable jugular venous distension upright with no Kussmaul sign, 3+ pitting edema to the knees, and bilateral crackles two-thirds up the lung fields. Cardiac examination shows a laterally displaced point of maximal intensity, a 2/6 systolic murmur at the apex and axilla, an S3, and no friction rub or pericardial knock. Which of the following is likely to reveal the most likely diagnosis?

A. Coronary angiography
B. Right heart catheterization
C. Serum polymerase chain reaction for *Trypanosoma cruzi* DNA
D. Serum *T. cruzi* IgG antibodies
E. Serum troponin

III-263. A 19-year-old woman returned 1 week ago from a month working in rural Bolivia for a nonprofit group. She had multiple bug bites and often woke up with open sores. One of these open sores has started to swell. She has a fever of 38°C. Because of her exposure history, you obtain a thin and thick blood smear that demonstrates organisms consistent with *Trypanosoma cruzi*. Which of the following is the best next intervention?

A. Immediate therapy with benznidazole
B. Immediate therapy with primaquine
C. Immediate therapy with voriconazole
D. Observation only
E. Serologic confirmation with specific *T. cruzi* IgG testing

III-264. A 44-year-old man who recently returned from a safari trip to Uganda seeks attention for a painful lesion on the leg and new fevers. He was on a safari tour where he stayed in the animal park that was populated extensively with antelope, lions, giraffes, and hippos. They often toured savannah and jungle settings. He returned within the last week and noticed a painful lesion on his neck at the site of some bug bites. He reports fever over 38°C, and you find palpable cervical lymphadenopathy. Review of systems is notable for malaise and anorexia for 2 days. A thick and thin smear of the blood reveals protozoa consistent with trypanosomes. All of the following are true about his disease EXCEPT:

A. Humans are the primary reservoir.
B. If untreated, death is likely.
C. It was transmitted by the bite of a tsetse fly.
D. Lumbar puncture should be performed.
E. Suramin is an effective treatment.

III-265. A 36-year-old man with HIV/AIDS is brought to the hospital after a grand mal seizure at home. He has a history of ongoing IV drug use and is not taking highly active antiretroviral therapy. His last CD4 T-cell count was <50/μL over a month ago. Further medical history is unavailable. Vital signs are normal. On examination he is barely arousable and disoriented. He is cachectic. There is no nuchal rigidity or focal motor deficit. Serum creatinine is normal. An urgent head MRI with gadolinium is performed, and the results of the T1-gated images are shown in Figure III-265. Which of the following will be the most effective therapy?

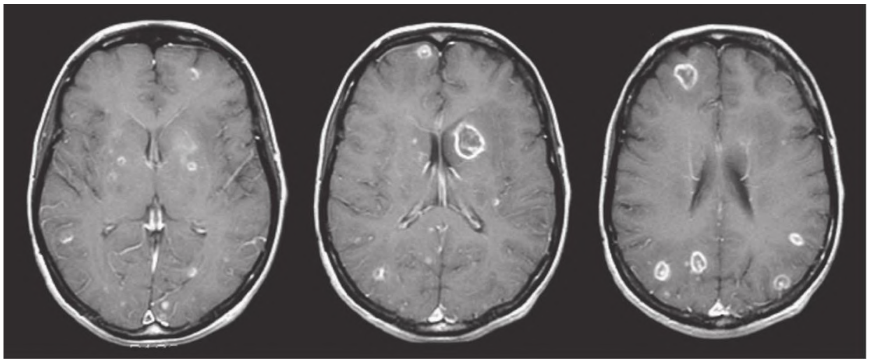


FIGURE III-265 Used with permission from Clifford Eskey, Dartmouth Hitchcock Medical Center, Hanover, NH.

A. Caspofungin
B. Isoniazid/rifampin/pyrazinamide/ethambutol
C. Pyrimethamine plus sulfadiazine
D. Streptokinase
E. Voriconazole

III-266. A 35-year-old woman with a past medical history of AIDS who is not currently on treatment presents with 2 weeks of watery diarrhea and weight loss. Stool samples are sent for antigen testing and return with *Cryptosporidium*. Which of the following is the best treatment option for her?

A. Albendazole
B. Nitazoxanide
C. Initiation of antiretroviral therapy
D. Metronidazole
E. Voriconazole

III-267. Which of the following intestinal protozoal infections can be diagnosed with stool ova and parasite examination?

A. *Cryptosporidium*
B. *Cyclospora*
C. *Giardia*
D. *Isospora*
E. *Microsporidia*

III-268. A 20-year-old sexually active woman presents with vaginal itchiness and malodorous discharge. A wet-mount microscopic examination demonstrates trichomonas parasites. Which of the following statements regarding trichomoniasis is true?

A. Most women are asymptomatic.
B. Trichomoniasis is commonly resistant to metronidazole.
C. Trichomoniasis is almost always spread sexually.
D. *Trichomonas vaginalis* almost never causes symptoms in men.
E. Wet prep is the most sensitive test for *T. vaginalis.*

III-269. A 19-year-old college student presents to the emergency department with crampy abdominal pain and watery diarrhea that has worsened over 3 days. He recently returned from a trip to Mexico. He has no past medical history and felt well throughout the trip. Stool examination shows small cysts containing four nuclei, and stool antigen immunoassay is positive for *Giardia*. Which of the following is a recommended treatment regimen for this patient?

A. Albendazole
B. Clindamycin
C. Giardiasis is self-limited and requires no antibiotic therapy
D. Paromomycin
E. Tinidazole

III-270. All of the following statements regarding the epidemiology of trichinellosis are true EXCEPT:

A. Cattle are a common source of trichinellosis infections.
B. Horse meat is a source of human trichinellosis.
C. Laws preventing the feeding of uncooked garbage to pigs have reduced the transmission of trichinellosis.
D. Most cases of trichinellosis are undiagnosed.
E. Recent outbreaks in the United States are primarily related to consumption of wild game.

III-271. A 42-year-old man in Montana presents to a clinic with progressive muscle weakness over the last few weeks. A month ago, he had gone on a bear hunting trip and ate some of the game. His symptoms started with nausea, vomiting, and diarrhea, followed by muscle weakness in his jaw and neck that has progressed to his arms and lower back. He also has decreased extraocular movements. On laboratory examination, his eosinophil level is markedly elevated as is his serum creatine phosphokinase. Which of the following organisms is the most likely cause of his symptoms?

A. *Campylobacter jejuni*
B. *Giardia*
C. Hepatitis A
D. *Taenia solium*
E. Trichinella

III-272. A 3-year-old boy presents to the clinic with recent fevers, anorexia, and weight loss. Most recently he has started wheezing at night. He had been completely healthy until these symptoms started 2 months ago. His family had traveled through Europe several months prior and reported no unusual exposures or exotic foods. They have a puppy at home. On examination, he is ill-appearing and is noted to have hepatosplenomegaly. Laboratory results show 82% eosinophils. Total white blood cell count is elevated. Which of the following is the most likely organism or process?

A. Cysticercosis
B. Giardiasis
C. *Staphylococcus lugdunensis*
D. Toxocariasis
E. Trichinellosis

III-273. The patient described in question III-272 continues to decline over the next 2–3 days, developing worsening respiratory status, orthopnea, and cough. On physical examination, his heart rate is 120 beats/min, blood pressure is 95/80, respiratory rate is 24 breaths/min, and oxygen saturation is 88% on room air. His neck veins are elevated, there is an apical S3, and his lungs have bilateral crackles half way up the lung fields. An echocardiogram shows an ejection fraction of 25%. Which of the following therapies should be initiated?

A. Albendazole
B. Methylprednisolone
C. Metronidazole
D. Nafcillin
E. Vancomycin

III-274. A 35-year-old man presents to the clinic with an intensely pruritic rash. He lives in the southeastern United States and recently had been cleaning the area under the porch of a house owned by a woman who fed multiple stray cats there. He was not wearing shoes. On examination his vital signs are normal. He has vesicular and bullous lesions on his feet (Figure III-274). Which of the following is causing his infection?

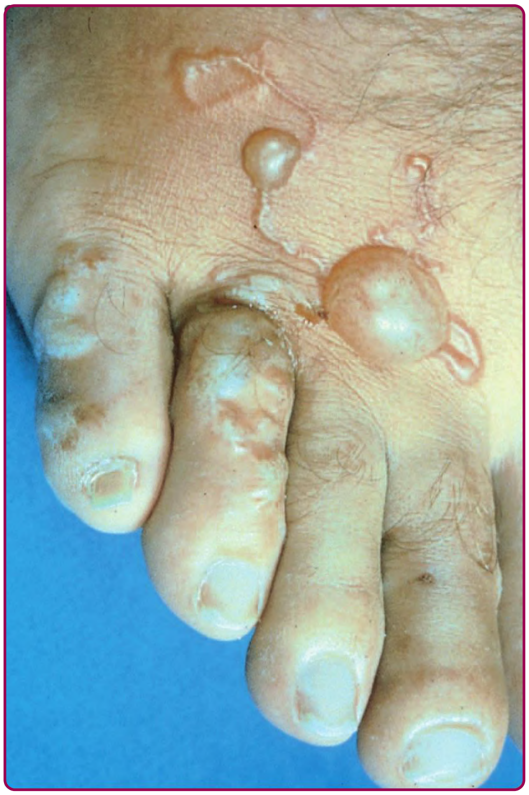


FIGURE III-274 Reproduced with permission from Kang S et al: *Fitzpatrick's Dermatology*, 9th ed. New York: McGraw Hill, 2019. Photo contributor: Jay S. Keystone, MD, FRCPC.

A. *Ancylostoma braziliense*
B. Toxocara
C. *Angiostrongylus cantonensis*
D. *Wuchereria bancrofti*
E. *Schistosoma mansoni*

III-275. A 32-year-old woman originally from Namibia is hospitalized for an asthma exacerbation and started on high-dose steroid treatment. As a child, she remembers having experienced several episodes of a serpiginous, raised, pruritic, and erythematous eruption on her legs. She becomes acutely ill 5 days into the high-dose steroid treatment, with fever, hypotension, tachycardia, shortness of breath, cough, abdominal pain, diarrhea, and nausea. Diffuse interstitial infiltrates are found on chest x-rays. Blood cultures return with *Escherichia coli*. A stool examination shows larvae. Which of the following is the likely cause of her condition?

A. *Ancylostoma duodenale*
B. *Ascaris lumbricoides*
C. *Enterobius vermicularis*
D. *Necator americanus*
E. *Strongyloides stercoralis*

III-276. All of the following are true of infection with *Ascaris lumbricoides* infection EXCEPT:

A. Adult worms typically cause no symptoms.
B. Association with hand-to-mouth fecal transmission.
C. Eosinophilia is usually found in asymptomatic infection.
D. Eosinophilic pneumonitis may be seen.
E. It may cause small bowel obstruction, especially in children.

III-277. A 21-year-old college student in Mississippi comes to student health to ask advice about treatment for *Ascaris* infection. He is an education major and works 1 day a week in an elementary school where a number of the students were recently diagnosed with ascariasis over the last 3 months. He feels well and reports being asymptomatic. A stool ova and parasite examination reveals characteristic Ascaris eggs. Which of the following should you recommend?

A. Albendazole
B. Diethylcarbamazine
C. Fluconazole
D. Metronidazole
E. No treatment

III-278. While on a business trip to Santiago, Chile, a 42-year-old woman presents to the emergency department with severe abdominal pain. She has no past medical or surgical history. She recalls no recent history of abdominal discomfort, diarrhea, melena, bright red blood per rectum, nausea, or vomiting prior to this acute episode. She ate ceviche (lime-marinated raw fish) at a local restaurant 3 hours prior to presentation. On examination, she is in terrible distress and has dry heaves. Temperature is 37.6°C, heart rate is 128 beats/min, and blood pressure is 174/92. Examination is notable for an extremely tender abdomen with guarding and rebound tenderness. Bowel sounds are present and hyperactive. Rectal examination is normal, and guaiac test is negative. Pelvic examination is unremarkable. White blood cell count is 6738/μL and hematocrit is 42%. A complete metabolic panel and lipase and amylase levels are all within normal limits. CT of the abdomen shows no abnormality. Which of the following is the next step in her management?

A. CT angiogram of the abdomen
B. Pelvic ultrasonography
C. Proton pump inhibitor therapy and observation
D. Right upper quadrant ultrasonography
E. Upper endoscopy

III-279. A 32-year-old male foreign services employee stationed in Jakarta, Indonesia, presents with fevers, groin pain, and a swollen scrotum for the past week. He uses no mosquito netting and travels frequently to jungles where he has had many mosquito bites. On examination, his temperature is 39.5°C. He has tender right inguinal lymphadenopathy with peripheral lymphatic streaking and significant scrotal swelling with a hydrocele (Figure III-279). Which of the following tests can you use to diagnose the patient?

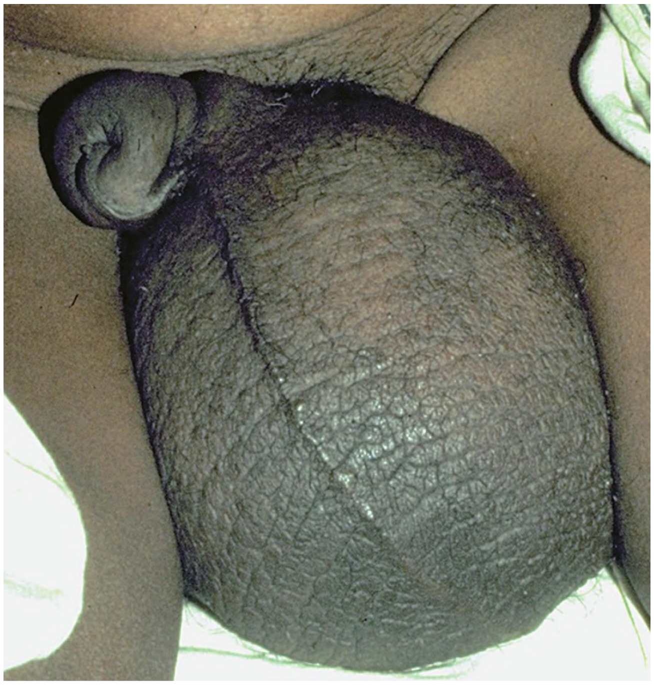


FIGURE III-279

A. Blood cultures
B. Rapid-format immunochromatographic card test for *Wuchereria bancrofti*
C. Serology tests for *W. bancrofti*
D. Stool ova and parasite examination
E. Urine cultures

III-280. In the patient described in question III-279, which of the following medications should be administered?

A. Albendazole
B. Diethylcarbamazine
C. Mebendazole
D. Metronidazole
E. Nitazoxanide

III-281. A 45-year-old woman is brought to the emergency department by her daughter because she saw something moving in her mother's eye. The patient is visiting from Congo where she lives in the rainforest. The patient reports some occasional eye swelling and redness. On examination, you find a worm in the subconjunctiva (Figure III-281). Which of the following medications is indicated for therapy?

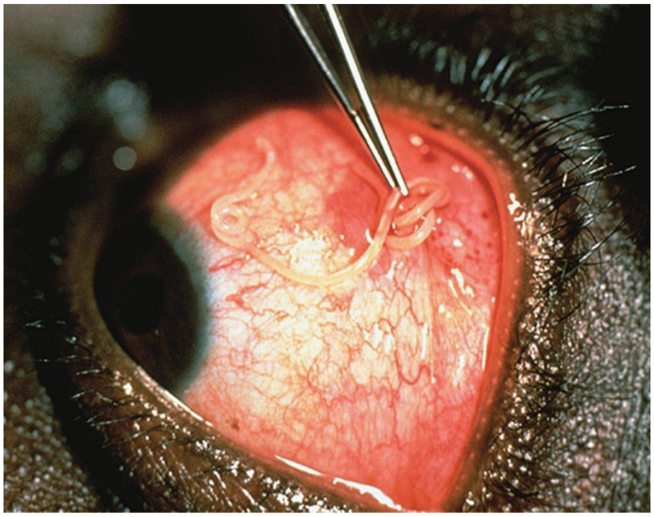


FIGURE III-281

A. Albendazole
B. Diethylcarbamazine
C. Ivermectin
D. Terbinafine
E. Voriconazole

III-282. All of the following statements regarding human schistosomal infections are true EXCEPT:

A. Adult worms are best detected in stool.
B. Infection is contracted through contact with freshwater harboring infected snails.
C. Schistosoma eggs cause the majority of morbidity from the infection.
D. *Schistosoma haematobium* causes urogenital disease.
E. *S. mansoni* causes intestinal disease.

III-283. A 48-year-old woman presents to her physician with a 2-day history of fever, arthralgias, diarrhea, and headache. She recently returned from an ecotour in tropical sub-Saharan Africa, where she went swimming in inland rivers. Notable findings on physical examination include a temperature of 38.7°C (101.7°F); 2-cm tender mobile lymph nodes in the axilla, cervical, and femoral regions; and a palpable spleen. Her white blood cell count is 15,000/μL with 50% eosinophils. She should receive treatment with which of the following medications?

A. Chloroquine
B. Mebendazole
C. Metronidazole
D. Praziquantel
E. Thiabendazole

III-284. A person with liver disease caused by *Schistosoma mansoni* would be most likely to have which of the following?

A. Ascites
B. Esophageal varices
C. Gynecomastia
D. Jaundice
E. Spider nevi

III-285. A 38-year-old woman originally from Honduras presents with a generalized seizure. She has no past medical history and no history of illicit drug or alcohol use. During her last pregnancy 1 year ago, she was documented to be HIV antibody negative, and 6 months prior to being hired at her current job she was noted to be purified protein derivative negative. A head CT shows multiple parenchymal lesions in both hemispheres (Figure III-285). She is started on anticonvulsant therapy. What additional medication should be started to manage her condition?

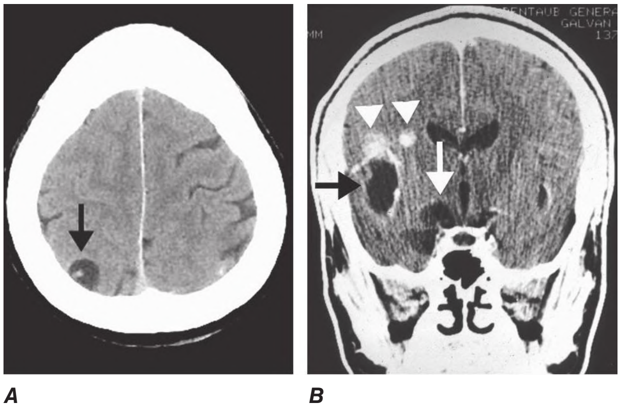


FIGURE III-285 (**B**) Reproduced with permission from Bandres JC et al: Extraparenchymal neurocysticercosis: report of five cases and review of management. *Clin Infect Dis* 15:799, 1992.

A. Albendazole and praziquantel
B. Ampicillin and ceftriaxone
C. Methicillin
D. Pyrimethamine and sulfadiazine
E. Vancomycin

III-286. A 44-year-old woman presents to the emergency department with recurrent episodes of right upper quadrant pain, typically soon after meals. These episodes have been present for at least a month and seem to be worsening. The patient emigrated from Lebanon over 20 years ago and works as an attorney. She takes no medications and is physically active. On examination, she is jaundiced and in obvious discomfort due to right upper quadrant pain. She is afebrile and tachycardic. Her physical examination is notable for an enlarged liver. Ultrasound examination confirms the large liver and demonstrates a complex 14-cm cyst with daughter cysts extending to the liver edge with associated biliary tract dilation (Figure III-286). Which of the following is the most appropriate management approach to this patient?

A. Albendazole medical therapy
B. Albendazole followed by surgical resection
C. Needle biopsy of the cystic lesion
D. Percutaneous aspiration, infusion of scolicidal agent, and re-aspiration
E. Serologic testing for *Echinococcus granulosus*

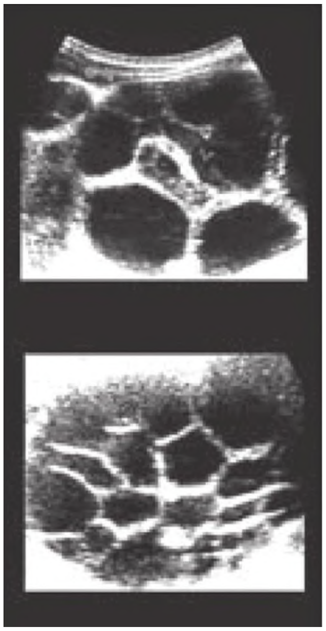


FIGURE III-286 Reproduced with permission from Guerrant RL et al: *Tropical Infectious Diseases: Principles, Pathogens and Practice*, 2nd ed. Philadelphia: Elsevier, 2005.

ANSWERS

III-1. **The answer is B.** *(Chap. 115)* Infectious diseases remain the second leading cause of death worldwide. Although the rate of infectious disease–related deaths has decreased dramatically over the past 25 years, there were still 10.9 million such deaths in 2013. These deaths disproportionately affect children <1 year of age, adults older than 70 years, and persons living in low- and middle-income countries. In 2013, 20% of all deaths worldwide were related to infectious diseases, with rates >50% in most sub-Saharan African countries (Figure III-1). Given that infectious diseases are still a major cause of global mortality, understanding the local epidemiology of disease is critically important in evaluating patients. Diseases such as HIV/AIDS have decimated sub-Saharan Africa, with HIV-infected adults representing 19–29% of the total population in countries like South Africa, Botswana, and Swaziland. Moreover, drug-resistant tuberculosis is rampant throughout the former Soviet-bloc countries, India, China, and South Africa. The ready availability of this type of information allows physicians to develop appropriate differential diagnoses and treatment plans for individual patients. Programs such as the Global Burden of Disease seek to quantify human losses (e.g., deaths, disability-adjusted life years) due to diseases by age, sex, and country over time. These data not only help inform local, national, and international health policy, but they can also help guide local medical decision-making.

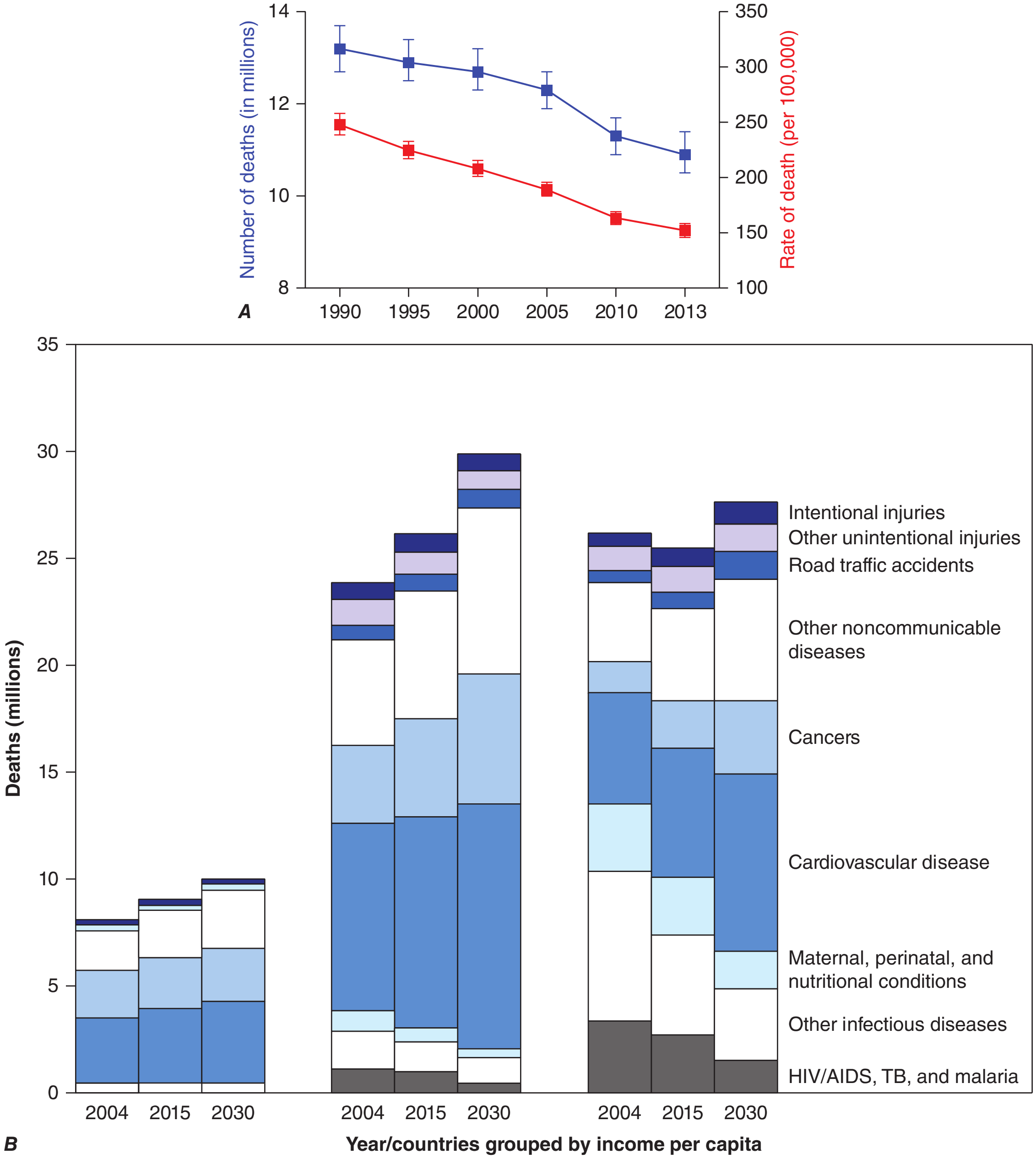


FIGURE III-1 ***(A)*** Magnitude of infectious disease–related deaths globally. The absolute number (*blue line; left axis*) and rate (*red line; right axis*) of infectious disease–related deaths throughout the world since 1990. ***(B)*** Projections of disease burden to 2030 for high-, middle-, and low-income countries (*left*, *center*, and *right*, respectively). TB, tuberculosis. (***A,*** Institute for Health Metrics and Evaluation. Used with permission. All rights reserved. ***B,*** Reproduced with permission from World Health Organization: The Global Burden of Disease 2004 Update, 2008.)

III-2. **The answer is B.** *(Chap. 115)* Given that elevations in temperature are often a hallmark of infection, paying close attention to the temperature may be of value in diagnosing an infectious disease. The idea that 37°C (98.6°F) is the normal human body temperature dates back to the 19th century and was initially based on axillary measurements. Rectal temperatures more accurately reflect the core body temperature and are 0.4°C (0.7°F) and 0.8°C (1.4°F) higher than oral and axillary temperatures, respectively. Although the definition of fever varies greatly throughout the medical literature, the most common definition, which is based on studies defining fever of unknown origin, uses a temperature ≥38.3°C (101°F). For every 1°C (1.8°F) increase in core temperature, the heart rate typically rises by 15–20 beats/min. Intracellular gram-negative bacteria, tick-borne organisms, and some viruses cause infections that may be associated with relative bradycardia (Faget sign), where patients have a lower heart rate than might be expected for a given body temperature (Table III-2). Although this pulse–temperature dissociation is not highly sensitive or specific for establishing a diagnosis, it is potentially useful in low-resource settings given its ready availability and simplicity.

TABLE III-2 Causes of Relative Bradycardia

Infectious Causes	
Intracellular organisms	
Gram-negative bacteria	*Salmonella typhi* *Francisella tularensis* *Brucella* spp. *Coxiella burnetii* (Q fever) *Leptospira interrogans* *Legionella pneumophila* *Mycoplasma pneumoniae*
Tick-borne organisms	*Rickettsia* spp. *Orientia tsutsugamushi* (scrub typhus) *Babesia* spp.
Other	*Corynebacterium diphtheriae* *Plasmodium* spp. (malaria)
Viruses/viral infections	Yellow fever virus Dengue virus Viral hemorrhagic fevers[a] Viral myocarditis
Noninfectious Causes	
	Drug fever Beta blocker use Central nervous system lesions Malignant lymphoma Factitious fever

[a] Primarily early in the course of infection with Marburg or Ebola virus.

III-3. **The answer is C.** *(Chap. 115)* The 1918 influenza pandemic spread through military maneuvers at the end of World War I. Even though some diseases (e.g., pandemic influenza, Middle East respiratory syndrome) are seemingly geographically restricted, the increasing ease of rapid worldwide travel has raised concern about their swift spread around the globe. Indeed, human migration has historically been the source of epidemics: *Yersinia pestis* spread along trade routes in the 14th century, Native American populations were devastated by diseases such as smallpox and measles that were imported by European explorers in the 15th and 16th centuries, military maneuvers helped facilitate the spread of the 1918 influenza pandemic, and religious pilgrimages (e.g., the Hajj) provide the means for worldwide dissemination of diseases. The introduction of cholera into Haiti, the transmission of Ebola within the United States, and the emerging outbreak of Zika virus infection are recent examples that highlight the continued effects of global travel on the spread of infectious diseases. Not only can travelers carry person-to-person transmitted infections (e.g., influenza, HIV) anywhere in the world, but they can also introduce vector-borne infections to new geographic areas (e.g., chikungunya and Zika viruses) and contribute to the worldwide spread of multidrug-resistant organisms. The world's increasing interconnectedness has profound implications not only for the global economy but also for medicine and the spread of infectious diseases. The current COVID-19 pandemic is an ongoing example of this phenomenon and clearly was propagated by international travel.

III-4. **The answer is D.** *(Chap. 116)* Results from the Human Microbiome Project suggest a high level of variability among individuals in microbiome components, although many individuals appear to maintain a fairly conserved microbiome throughout their lives. Indigenous microbial organisms live in close association with almost all animals, and plants are organized into complex communities that strongly modulate overall host physiology, including the ability of pathogenic microbes to establish themselves in or on host surfaces. The sheer numbers of these microbes and their genomic variability often exceed the numbers of host cells and the variability of host genes in a typical animal. Changes and differences in microbiomes within and between individuals, currently characterized by high-throughput DNA sequencing techniques and bioinformatic analysis, impact such diverse conditions as obesity; type 1 diabetes; cognition; neurologic states; autoimmune diseases; skin, gastrointestinal, respiratory, and vaginal infectious diseases; and development and control of the immune system. One of the clearest functions of the microbiota is to influence and mature the cells of the immune system, exerting a major effect on susceptibility and resistance to microbial infection. The degree to which studies of the microbiome will translate into strategies for the management of human health and disease is still an open question; however, the use of fecal transplants to treat and prevent recurrences of serious *Clostridioides difficile* infection is established. In the context of infectious diseases, changes and disruptions of the indigenous microbiome—i.e., alterations of the normal flora due to antibiotic and immunosuppressive drug use, environmental changes, and the effects of microbial virulence factors used to displace the indigenous microbial flora and thus to facilitate pathogen colonization—have a strong and often fundamental impact on the progression of infection. While the technology for defining and understanding the microbiome is still quite young, there is little doubt that the resulting data will markedly affect our concepts of and approaches to microbial pathogenesis and infectious disease treatment.

III-5. and III-6. **The answers are A and E, respectively.** *(Chap. 117)* Individuals who have had a splenectomy are at increased risk for death due to sepsis, with a death rate 58 times higher than that of the general population. Most infections occur within the first 2 years after splenectomy, but the risk remains higher than the general population throughout life despite vaccination. Mortality from sepsis in an individual who has undergone splenectomy is about 50%. The most common organism causing sepsis in individuals who have had splenectomy is *Streptococcus pneumoniae* (option E), which is responsible for 50–70% of cases of sepsis in asplenic patients. Other organisms with a high incidence of sepsis in asplenic patients include *Haemophilus influenzae* (option B) and *Neisseria meningitidis* (option C), although these are less common than *S. pneumoniae.* The recommended initial empiric antibiotics for individuals with postsplenectomy sepsis are ceftriaxone 2 g IV every 12 hours and vancomycin 15 mg/kg every 12 hours.

III-7. **The answer is B.** *(Chaps. 117 and 159)* Ecthyma gangrenosum is a typical rash marked by hemorrhagic vesicles surrounded by a rim of erythema with central necrosis and ulceration. This finding is seen in sepsis caused by *Pseudomonas aeruginosa* most commonly and can be seen with *Aeromonas hydrophila*. Sepsis due to these organisms most frequently occurs in individuals with prolonged neutropenia, extensive burns, or hypogammaglobulinemia.

III-8. **The answer is B.** *(Chaps. 117 and 163)* The patient has sepsis caused by *Vibrio vulnificus*. *V. vulnificus* and other non-cholera *Vibrio* bacteremic infections can cause focal skin lesions and overwhelming sepsis in hosts with chronic liver disease, heavy alcohol consumption, iron storage disorders, diabetes, renal insufficiency, hematologic disease, or malignancy or other immunocompromising conditions. After ingestion of contaminated raw shellfish (typically oysters from the Gulf Coast in U.S. cases), there is a sudden onset of malaise, chills, fever, and hypotension. The patient develops bullous or hemorrhagic skin lesions, usually on the lower extremities, and 75% of patients have leg pain. The mortality rate can be as high as 50–60%, particularly when the patient presents with hypotension. Per the Centers for Disease Control and Prevention, first-line therapy includes doxycycline with ceftriaxone. However, in animal models, single-agent regimens containing a fluoroquinolone (option A) may be equally effective as a tetracycline with a third-generation cephalosporin. Other infections, caused by agents such as *Aeromonas*, *Klebsiella*, and *Escherichia coli*, can cause hemorrhagic bullae and death due to overwhelming sepsis in cirrhotic patients.

III-9. **The answer is C.** *(Chaps. 117 and 149)* This patient has necrotizing fasciitis. Her renal disease and malignancy are associated risk factors. Physical findings are initially minimal compared with the severity of pain and the degree of fever. The examination is often unremarkable except for soft tissue edema and erythema. The infected area is red, hot, shiny, swollen, and exquisitely tender. In untreated infection, the overlying skin develops blue-gray patches after 36 hours, and cutaneous bullae and necrosis develop after 3–5 days. Necrotizing fasciitis due to a mixed flora, but not due to group A streptococci, can be associated with gas production. Without treatment, pain decreases because of thrombosis of the small blood vessels and destruction of the peripheral nerves, which is an ominous sign. The mortality rate is 15–34% overall, >70% in association with toxic shock syndrome (TSS), and nearly 100% without surgical intervention. Necrotizing fasciitis may also be due to *Clostridium perfringens*; in this condition, the patient is extremely toxic and the mortality rate is high. Within 48 hours, rapid tissue invasion and systemic toxicity associated with hemolysis and death ensue. The distinction between this entity and clostridial myonecrosis is made by muscle biopsy. Necrotizing fasciitis caused by community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) also has been reported. Necrotizing fasciitis, formerly called streptococcal gangrene, may be associated with group A *Streptococcus* or mixed aerobic–anaerobic bacteria or may occur as a component of gas gangrene caused by *C. perfringens*. Strains of MRSA that produce the Panton-Valentine leukocidin toxin have been reported to cause necrotizing fasciitis. Early diagnosis may be difficult when pain or unexplained fever is the only presenting manifestation. Swelling then develops and is followed by brawny edema and tenderness. With progression, dark-red induration of the epidermis appears, along with bullae filled with blue or purple fluid. Later the skin becomes friable and takes on a bluish, maroon, or black color. By this stage, thrombosis of blood vessels in the dermal papillae is extensive. Extension of infection to the level of the deep fascia causes this tissue to take on a brownish-gray appearance. Rapid spread occurs along fascial planes, through venous channels and lymphatics. Patients in the later stages are toxic and frequently manifest shock and multiorgan failure. Early and aggressive surgical exploration is essential in cases of suspected necrotizing fasciitis, myositis, or gangrene to (1) visualize the deep structures, (2) remove necrotic tissue, (3) reduce compartment pressure, and (4) obtain suitable material for Gram staining and for aerobic and anaerobic cultures. Appropriate empirical antibiotic treatment should target mixed aerobic-anaerobic infections, including *Staphylococcus*. In experimental models of streptococcal and clostridial necrotizing fasciitis/myositis, clindamycin has exhibited markedly superior efficacy, but no comparative clinical trials have been performed. A retrospective study of children with invasive group A streptococcal infection demonstrated higher survival rates with clindamycin treatment than with β-lactam antibiotic therapy. Hyperbaric oxygen treatment also may be useful in gas gangrene due to clostridial species. Antibiotic treatment should be continued until all signs of systemic toxicity have resolved, all devitalized tissue has been removed, and granulation tissue has developed.

III-10. and III-11. **The answers are B and B, respectively.** (*Chap. 118,* https://www.cdc.gov/measles/cases-outbreaks.html) Measles and pertussis are two vaccine-preventable illnesses that are making a remarkable reemergence in the United States. Prior to the availability of the combined measles, mumps, and rubella (MMR) vaccine, there were more than 500,000 cases of measles yearly. By 2012, the disease had nearly been eliminated in the United States, with only 55 reported cases; however, by 2019, the number of cases increased to 1282. The disease is still considered to be eliminated in the United States with no indigenous transmission of the disease because all new cases of the disease arise from importation of the disease from countries outside of the United States. The 2019 outbreaks threatened this status. The largest outbreaks that occurred in 2019 were two interconnected outbreaks in New York State and New York City among large, close-knit Orthodox Jewish communities, accounting for 75% of the total outbreak. When one considers all individuals affected in a measles outbreak, the primary individuals who are affected (89% in the 2019 outbreak) are those who are unvaccinated for philosophical or religious beliefs. All components of the MMR vaccine are live attenuated virus, but there are no reports of spontaneous mutation to a virulent form. After two doses of vaccine, >95% of individuals above 1 year of age are immune from measles.

III-12. **The answer is B.** *(Chap. 118)* Pneumococcal vaccination has been recommended for all individuals at any age with a variety of chronic medical conditions, including chronic respiratory disease, chronic heart disease, chronic liver failure, diabetes mellitus, asplenia, and chronic kidney disease. Determining when to revaccinate individuals has been somewhat controversial. The current recommendations are to revaccinate individuals ages 19 to 64 years old 5 years after the initial vaccine if they have chronic renal failure or nephrotic syndrome, asplenia, or other immunocompromising conditions. All other individuals should receive a one-time revaccination at age 65 and older if they were vaccinated 5 or more years previously and were age less than 65 at the time of original vaccination.

III-13. **The answer is A.** *(Chap. 118)* The varicella-zoster vaccine is a live-virus vaccine. Live-virus vaccines are contraindicated during pregnancy because of the hypothetical risk that vaccine virus replication will cause congenital infection or have other adverse effects on the fetus. Most live-virus vaccines, including varicella vaccine, are not secreted in breast milk; therefore, breastfeeding is not a contraindication for live-virus or other vaccines (option D). Pregnancy is not a contraindication to administration of inactivated vaccines, but most are avoided during pregnancy because relevant safety data are limited. Two inactivated vaccines, tetanus/diphtheria/pertussis (Tdap) vaccine and inactivated influenza vaccine, are routinely recommended for pregnant women in the United States (options B and C). Tdap vaccine is recommended during each pregnancy, regardless of prior vaccination status, to prevent pertussis in neonates. Annual influenza vaccination is recommended for all persons 6 months of age and older, regardless of pregnancy status. Some other inactivated vaccines, such as meningococcal vaccines, may be given to pregnant women in certain circumstances (option E). It is important to note that mild acute illnesses are not contraindications to vaccination (option E).

III-14. **The answer is E.** *(Chap. 119)* When traveling abroad, it is important to plan ahead and consider the potential infectious agents to which one might be exposed. The Centers for Disease Control and Prevention and the World Health Organization publish guidelines for recommended vaccinations prior to travel to countries around the world. Immunizations for travel fall into three broad categories: *routine* (childhood/adult immunizations and boosters that are important regardless of travel), *required* (immunizations that are mandated by international regulations for entry into certain areas or for border crossings), and *recommended* (immunizations that are desirable because of travel-related risks). Of this list, yellow fever is the only required vaccination for entry into many countries in sub-Saharan Africa. Documentation of vaccination against yellow fever may be required or recommended as a condition for entry into or passage through countries of sub-Saharan Africa and equatorial South America, where the disease is endemic or epidemic, or (according to the International Health Regulations) for entry into countries at risk of having the infection introduced. Meningococcal vaccination (option C) is not required for entry into countries in sub-Saharan Africa. However, protection against meningitis is required for entry into Saudi Arabia during the Hajj. Hepatitis A (option B) is one of the most common vaccine-preventable infections of travelers and is therefore strongly recommended, but it is not required prior to travel. Vaccination for typhoid fever (option D) is also recommended but not required. A live oral cholera vaccine (option A) was recently approved in the United States by the U.S. Food and Drug Administration. Its use should be considered for aid and health care workers in refugee camps or in disaster-stricken/war-torn areas. Prior to travel, it is certainly recommended that an individual be up to date on all routine vaccinations, including measles, diphtheria, and polio. Influenza is perhaps the most common preventable illness in travelers, and the influenza vaccine should be administered per routine guidelines.

III-15. **The answer is B.** (*Chap. 119,* https://wwwnc.cdc.gov/travel/yellowbook/2020/travel-related-infectious-diseases/malaria) It is estimated that >30,000 American and European travelers develop malaria each year. The risk to travelers is highest in Oceania and sub-Saharan Africa (estimated at 1:5 and 1:50 per month of stay, respectively, among persons not using chemoprophylaxis), intermediate in malarious areas on the Indian subcontinent and in Southeast Asia (1:250–1:1000 per month), and low in South and Central America (1:2500–1:10,000 per month). With the worldwide increase in chloroquine-resistant and multidrug-resistant falciparum malaria, decisions about chemoprophylaxis have become more difficult (Table III-15). The Centers for Disease Control and Prevention note that malaria is present in all areas of Kenya at altitudes lower than 2500 m including game parks and Nairobi. *Falciparum malaria* in sub-Saharan Africa is commonly resistant to chloroquine, so this option would not be a preferred prophylactic regimen.

TABLE III-15 Malaria Chemosuppressive Regimens, According to Geographic Area[a]

Geographic Area	Drug of Choice[b]	Alternatives
Central America (north of Panama), Iraq, Turkey, northern Argentina, and Paraguay	Chloroquine	Atovaquone-proguanil[c] Doxycycline Mefloquine Primaquine
South America (but not northern Argentina or Paraguay, where chloroquine may be used), Central America (only Panama east of the Canal), Asia (including Southeast Asia), Africa, and Oceania	Doxycycline Atovaquone-proguanil[c] Mefloquine	
Thai–Myanmar and Thai–Cambodian borders, central Vietnam	Atovaquone-proguanilc Doxycycline	

[a] See the Centers for Disease Control and Prevention's *Health Information for International Travel 2018* (www.cdc.gov/travel).

[b] In all areas where chloroquine can still be used, the other drugs listed may be used as alternatives.

[c] Malarone.

Note: See also Chap. 219 in HPIM 20.

III-16. The answer is D. (*Chap. 119,* https://wwwnc.cdc.gov/travel/destinations/clinician/none/haiti?s_cid=ncezid-dgmq-travel-single-002) Hepatitis A (option E) is one of the most common vaccine-preventable infections of travelers. Since the most frequently identified risk factor for hepatitis A in the United States is international travel, and since morbidity and mortality risk increase with age, it seems appropriate that all adults be immune prior to travel. Malaria is also endemic in Haiti. Although there is a worldwide increase in chloroquine-resistant falciparum malaria, malaria in Haiti does continue to be susceptible to chloroquine, so chloroquine is a recommended prophylaxis option (option A). In addition, keys to the prevention of malaria as well as other mosquito-transmitted illnesses prevalent in Haiti, such as dengue, chikungunya, and Zika also include personal protection measures against mosquito bites (especially between dusk and dawn). Examples of these personal protective measures include the use of diethyltoluamide (DEET) or picaridin-containing insect repellents (option C), permethrin-impregnated bed nets and clothing, screened sleeping accommodations, and protective clothing. In general, higher concentrations of any active ingredient provide a longer duration of protection. However, studies suggest that concentrations of DEET above ~50% do not offer a marked increase in protection time against mosquitoes. The Centers for Disease Control and Prevention also recommends oil of lemon eucalyptus (para-menthane-3,8-diol) (option B) and IR3535 (3-[*N*-butyl-*N*-acetyl]-aminopropionic acid ethyl ester). Regardless of travel, pneumococcal vaccine (option D) should be administered routinely to all persons aged >65 and to persons between the ages of 2 and 64 who are at high risk of serious infection, including those with diabetes mellitus; those with chronic heart, lung, or kidney disease; those who have been splenectomized or are immunocompromised; and those who have sickle cell disease. However, in this healthy 28-year-old man, the pneumococcal vaccine would not be recommended.

III-17. The answer is E. *(Chap. 120)* The release of greenhouse gases, principally carbon dioxide, into Earth's atmosphere since the late 19th century has contributed to a climate unfamiliar to our species, *Homo sapiens*. This new climate has already altered the epidemiology of some infectious diseases. Continued accumulation of greenhouse gases in the atmosphere will further alter the planet's climate. In some cases climate change may establish conditions favoring the emergence of infectious diseases, while in others it may render areas that are presently suitable for certain diseases unsuitable. Higher temperatures promote higher mosquito-biting rates, shorter parasite reproductive cycles, and the potential for the survival of mosquito vectors of *Plasmodium* infection in locations previously too cold to sustain them. Climate change may create conditions favorable for malaria in subtropical and temperate regions of the Americas, Europe, and Asia. In the last few decades, *Ixodes scapularis*, the primary tick vector for Lyme disease as well as for anaplasmosis and babesiosis in New England, has become established in Canada because of warming temperatures (Figure III-17). Although no clear safety threshold of greenhouse gas emissions has been agreed on, national governments from the major industrialized countries have

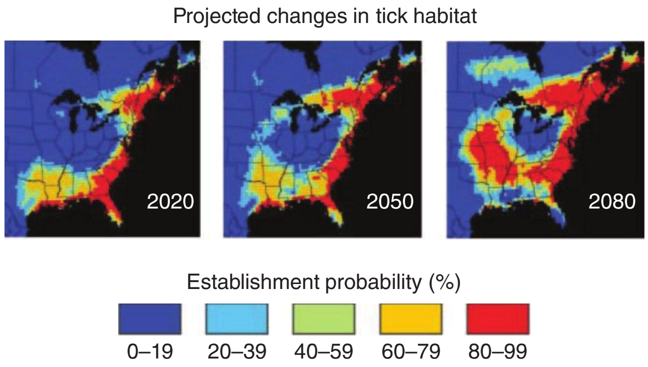

Projected changes in tick habitat
2020
2050
2080
Establishment probability (%)
0–19
20–39
40–59
60–79
80–99

FIGURE III-17 Present and projected probability of establishment of *Ixodes scapularis.* (Reproduced with permission from Brownstein JS et al: Effect of climate change on Lyme disease risk in North America. *Ecohealth* 2:38, 2005.)

agreed to set a warming target of <2°C above preindustrial levels by 2050; the attainment of this goal will require reducing greenhouse gas emissions by 40–70% below 2010 levels.

III-18. The answer is C. (*Chap. 121,* https://www.atsjournals.org/doi/full/10.1164/rccm.201908-1581ST) There is an extensive list of potential etiologic agents in community-acquired pneumonia (CAP) including bacteria, fungi, viruses, and protozoa. However, most cases of CAP are caused by relatively few pathogens. *Streptococcus pneumoniae* is the most common cause of CAP, and 10–15% of cases are polymicrobial. The most common causes of CAP in outpatients are *S. pneumoniae*, *Mycoplasma pneumoniae*, *Haemophilus influenzae*, *Chlamydia pneumoniae*, and respiratory viruses. In hospitalized patients that are not in the intensive care unit (ICU), this list also includes *Legionella* species. The most common microbial causes of CAP in patients treated in the ICU are *S. pneumoniae*, *Staphylococcus aureus*, *Legionella* species, gram-negative bacilli, and *H. influenzae.*

III-19. The answer is D. (*Chap. 121,* https://www.atsjournals.org/doi/full/10.1164/rccm.201908-1581ST) Determining the appropriate initial treatment for community-acquired pneumonia (CAP) initially requires determining whether the severity of illness warrants admission to the hospital. Clinical rules for determining potential severity of pneumonia have been developed including the Pneumonia Severity Index (PSI) and the CURB-65 criteria. Although the PSI has the largest body of research to support its use, and is the recommended clinical prediction rule for determining inpatient versus outpatient management of CAP in the Infectious Diseases Society of America/American Thoracic Society 2019 CAP guidelines, the model includes 20 variables that may be impractical to implement in a busy clinical practice. The CURB-65 criteria include only five variables: (1) confusion, (2) urea >7 mmol/L, (3) respiratory rate ≥30 breaths/min, (4) blood pressure ≤90/60, and (5) age ≥65. This patient meets none of these criteria and is not hypoxemic or in a high-risk group for complications from CAP. Therefore, he can safely be treated as an outpatient without further diagnostic workup as his history, physical examination, and chest radiograph are all consistent with the diagnosis of CAP. The empiric antibiotic regimen recommended by the Infectious Diseases Society of America/American Thoracic Society in the 2019 CAP guidelines for individuals who are previously healthy and do not have risk factors for methicillin-resistant *Staphylococcus aureus* (MRSA) or *Pseudomonas* infection is either amoxicillin or doxycycline. In regions of the country where pneumococcus resistance to macrolides (<25%) is low, macrolides such as azithromycin or clarithromycin are also recommended. In outpatients with significant medical comorbidities or risk factors for MRSA or *Pseudomonas* infection within 3 months, the suggested antibiotics are either (1) a respiratory fluoroquinolone (such as moxifloxacin or levofloxacin) or (2) a β-lactam (amoxicillin-clavulanate, cefpodoxime, or cefuroxime) plus a macrolide or doxycycline.

III-20. The answer is E. *(Chap. 121)* Pneumonia is a common complication among patients requiring mechanical ventilation. Prevalence estimates vary between 6 and 52 cases per

100 patients, depending on the population studied. On any given day in the intensive care unit (ICU), an average of 10% of patients will have pneumonia ventilator-associated pneumonia (VAP) in the overwhelming majority of cases. The frequency of diagnosis is not static but changes with the duration of mechanical ventilation, with the highest hazard ratio in the first 5 days and a plateau in additional cases (1% per day) after ~2 weeks. However, the cumulative rate among patients who remain ventilated for as long as 30 days is as high as 70%. No single set of criteria is reliably diagnostic of pneumonia in a ventilated patient. The inability to accurately identify such patients compromises efforts to prevent and treat VAP and even calls into question estimates of the impact of VAP on mortality rates. Application of the clinical criteria typical for community-acquired pneumonia consistently results in overdiagnosis of VAP, largely because of three common findings in at-risk patients: (1) frequent tracheal colonization with pathogenic bacteria in patients with endotracheal tubes, (2) multiple alternative causes of radiographic infiltrates in mechanically ventilated patients, and (3) the high frequency of other sources of fever in critically ill patients. The differential diagnosis of VAP includes a number of entities such as atypical pulmonary edema, pulmonary contusion, alveolar hemorrhage, hypersensitivity pneumonitis, acute respiratory distress syndrome, and pulmonary embolism. Clinical findings in ventilated patients with fever and/or leukocytosis may have alternative causes, including antibiotic-associated diarrhea, central line–associated infection, sinusitis, urinary tract infection, pancreatitis, and drug fever. Conditions mimicking pneumonia are often documented in patients in whom VAP has been ruled out by accurate diagnostic techniques. Most of these alternative diagnoses do not require antibiotic treatment; require antibiotics different from those used to treat VAP; or require some additional intervention, such as surgical drainage or catheter removal, for optimal management. This diagnostic dilemma has led to debate and controversy. The major question is whether a quantitative-culture approach as a means of eliminating false-positive clinical diagnoses is superior to the clinical approach enhanced by principles learned from quantitative-culture studies. The most recent Infectious Diseases Society of America/American Thoracic Society guidelines for hospital-acquired pneumonia/VAP gave a weak recommendation for the clinical approach based on availability of resources, cost, and availability of expertise. The guidelines did acknowledge that the use of a quantitative approach may result in less antibiotic use, which may be critical for antibiotic stewardship in the ICU. Therefore, the approach at each institution, or potentially for each patient, should balance the frequency of complex illnesses that are associated with (1) greater frequency of alternative causes of the clinical manifestations, (2) higher colonization rates, and (3) more frequent prior antibiotic therapy versus availability and expertise of invasive techniques with quantitative cultures.

III-21. **The answer is C.** *(Chap. 121)* Pleural effusion is a known complication of severe community-acquired pneumonia. A significant pleural effusion should be tapped for both diagnostic and therapeutic purposes. If the fluid has a pH of <7, a glucose level of <2.2 mmol/L, and a lactate dehydrogenase concentration of >1000 U/L or if bacteria are seen or cultured, it should be completely drained; a chest tube is often required, and video-assisted thoracoscopy may be needed for late treatment or difficult cases. An elevated pleural fluid protein alone may not require additional intervention.

III-22. **The answer is B.** *(Chap. 121)* Patients were previously treated for community-acquired pneumonia (CAP) for 10–14 days, but studies have suggested that a 5-day course is sufficient for otherwise uncomplicated CAP. Longer cases may be required for patients with bacteremia or virulent pathogens such as *Pseudomonas aeruginosa* or methicillin-resistant *Staphylococcus aureus*. Decreased duration of antibiotic therapy leads to decreased antibiotic resistance and decreased likelihood of adverse effects.

III-23. **The answer is D.** *(Chap. 122)* Lung abscess represents necrosis and cavitation of the lung following microbial infection, and are often caused by anaerobic bacteria but are often polymicrobial. The major risk factor for primary lung abscesses is aspiration. Patients at particular risk for aspiration, such as those with altered mental status, alcoholism, drug overdose, seizures, bulbar dysfunction, prior cerebrovascular or cardiovascular events, or neuromuscular disease, are most commonly affected. In addition, patients with esophageal dysmotility or esophageal lesions (strictures or tumors) and those with gastric distention and/or gastroesophageal reflux, especially those who spend substantial time in the recumbent position, are at risk for aspiration. For primary lung abscesses, the recommended therapeutic regimens are either ampicillin-sulbactam (transitioned to oral amoxicillin-clavulanate once the patient is stable) or clindamycin. However, given risks of clindamycin including *Clostridioides difficile* infection, ampicillin-sulbactam may be preferred. Primary lung abscesses are often >2 cm and are typically treated empirically with antibiotics, but an abscess >6–8 cm in diameter is less likely to respond to antibiotic therapy without additional interventions. Options for patients who do not respond to antibiotics and whose additional diagnostic studies fail to identify an additional pathogen that can be treated include surgical resection and percutaneous drainage of the abscess. The dependent segments (posterior upper lobes and superior lower lobes) of the lung are the most common locations of primary lung abscesses, given the predisposition of aspirated materials to be deposited in these areas. Generally, the right lung is affected more commonly than the left because the right mainstem bronchus is less angulated.

III-24. The answer is A. *(Chap. 122)* This patient has a typical right lower lobe lung abscess likely related to alcoholism and aspiration. The history of a few weeks of illness with constitutional findings is typical. The radiograph shows an abscess with air-fluid level in the right lower lobe. Therapy should be directed to the upper airway anaerobic bacteria. For primary lung abscesses, the recommended regimens are either ampicillin-sulbactam (transitioned to oral amoxicillin-clavulanate once the patient is stable) or clindamycin. However, given risks of clindamycin including *Clostridioides difficile* infection, ampicillin-sulbactam may be preferred. Antibiotic therapy should be continued until imaging demonstrates that the lung abscess has cleared or regressed to a small scar. Treatment duration may range from 3–4 weeks to as long as 14 weeks. One small study suggested that moxifloxacin (400 mg/d PO) is as effective and well tolerated as ampicillin-sulbactam. Notably, metronidazole is not effective as a single agent; it covers anaerobic organisms but not the microaerophilic streptococci that are often components of the mixed flora of primary lung abscesses. Aztreonam has predominant activity against gram-negative bacteria, and micafungin is an antifungal agent; neither has activity against oral anaerobes. Penicillin is traditional therapy for lung abscess but is not as effective as ampicillin-sulbactam or clindamycin.

III-25. The answer is E. *(Chap. 123)* The etiologic agents of infective endocarditis vary by host (Table III-25). In developed countries, 40% of native valve endocarditis (NVE) not associated with injection drug use is caused by *Streptococcus*. Health care–associated NVE, most commonly caused by *Staphylococcus aureus*, coagulase-negative staphylococci (CoNS), and enterococci, may have either a nosocomial onset (55%) or a community onset (45%) in patients who have had extensive contact with the health care system. Injection drug use–associated endocarditis, especially that involving the tricuspid valve, is commonly caused by *S. aureus*, which in many cases is resistant to methicillin. Left-sided valve infections in drug-addicted patients have a more varied etiology. In addition to the usual causes of endocarditis, these cases can be due to *Pseudomonas aeruginosa* and *Candida* species, and sporadic cases can be caused by unusual organisms such as *Bacillus*, *Lactobacillus*, and *Corynebacterium* species. Polymicrobial endocarditis occurs among injection drug users. HIV infection in drug users does not significantly influence the causes of endocarditis.

TABLE III-25 Organisms Causing Major Clinical Forms of Endocarditis

	Percentage of Cases								
	Native-Valve Endocarditis		Prosthetic-Valve Endocarditis at Indicated Time of Onset (Months) after Valve Surgery			Endocarditis in Injection Drug Users			
Organism(s)	Community-Acquired (*n* = 1718)	Health Care–Associated (*n* = 1110)	<2 (*n* = 144)	2–12 (*n* = 31)	>12 (*n* = 194)	Right-sided (*n* = 346)	Left-sided (*n* = 204)	Total (*n* = 675)[a]	CIED (*n* = 337)
Streptococci[b]	40	13	1	9	31	5	15	12	2
Pneumococci	2	—	—	—	—	—	—	—	—
Enterococci[c]	9	16	8	12	11	2	24	9	4
Staphylococcus aureus	28	52[d]	22	12	18	77	23	57	36
Coagulase-negative staphylococci	5	11	33	32	11	—	—	—	41
Fastidious gram-negative coccobacilli (HACEK group)[e]	3	—	—	—	6	—	—	—	—
Gram-negative bacilli	1	1	13	3	6	5	13	7	6
Candida spp.	<1	1	8	12	1	—	12	4	2
Polymicrobial/ miscellaneous	3	3	3	6	5	8	10	7	2
Diphtheroids	—	<1	6	—	3	—	—	0.1	1
Culture-negative	9	3	5	6	8	3	3	3	6

[a] The total number of cases is larger than the sum of right- and left-sided cases because the location of infection was not specified in some cases.

[b] Includes viridans streptococci; *Streptococcus gallolyticus*; other non–group A, groupable streptococci; and *Abiotrophia* and *Granulicatella* spp. (nutritionally variant, pyridoxal-requiring streptococci).

[c] Primarily *Enterococcus faecalis* or nonspeciated isolates; occasionally *E. faecium* or other, less likely species.

[d] Methicillin resistance is common among these *S. aureus* strains.

[e] Includes *Haemophilus* spp., *Aggregatibacter* spp., *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*.

Abbreviation: CIED, cardiac implantable electronic device.

Note: Data are compiled from multiple studies.

III-26. The answer is B. *(Chap. 123)* The Modified Duke Criteria are a highly sensitive and specific diagnostic schema based on clinical, laboratory, and echocardiographic findings commonly encountered in patients with endocarditis (Table III-26). Documentation of two major criteria, of one major criterion and three minor criteria, or of five minor criteria allows a clinical diagnosis of definite endocarditis. Evidence of echocardiographic involvement as evidenced by an oscillating mass (vegetation) on a valve, supporting structure, or implanted material; an intracardiac abscess, partial dehiscence of a prosthetic valve; or new valvular regurgitation is a major criterion in the Duke classification. An increase or change in pre-existing murmur by clinical examination is not sufficient. Transthoracic echocardiography is specific for infective endocarditis but only finds vegetations in about 65% of patients with definite endocarditis. It is not adequate for evaluation of prosthetic valves or for intracardiac complications. Transesophageal echocardiography is more sensitive, detecting abnormalities in >90% of cases of definite endocarditis.

TABLE III-26 The Modified Duke Criteria for the Clinical Diagnosis of Infective Endocarditis[a]

Major Criteria

1. Positive blood culture
   - Typical microorganism for infective endocarditis from two separate blood cultures
     - Viridans streptococci, *Streptococcus gallolyticus*, HACEK group organisms, *Staphylococcus aureus*, ***or***
     - Community-acquired enterococci in the absence of a primary focus,
     - ***or***
   - Persistently positive blood culture, defined as recovery of a microorganism consistent with infective endocarditis from:
     - Blood cultures drawn >12 h apart; ***or***
     - All of 3 or a majority of ≥4 separate blood cultures, with first and last drawn at least 1 h apart
     - ***or***
   - Single positive blood culture for *Coxiella burnetii* or phase I IgG antibody titer of >1:800
2. Evidence of endocardial involvement
   - Positive echocardiogram[b]
     - Oscillating intracardiac mass on valve or supporting structures or in the path of regurgitant jets or in implanted material, in the absence of an alternative anatomic explanation, ***or***
     - Abscess, ***or***
     - New partial dehiscence of prosthetic valve,
     - ***or***
   - New valvular regurgitation (increase or change in preexisting murmur not sufficient)

Minor Criteria

1. Predisposition: predisposing heart conditions[c] or injection drug use
2. Fever ≥38.0°C (≥100.4°F)
3. Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions
4. Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, rheumatoid factor
5. Microbiologic evidence: positive blood culture but not meeting major criterion, as noted previously,[d] ***or*** serologic evidence of active infection with an organism consistent with infective endocarditis

[a] Definite endocarditis is defined by documentation of two major criteria, of one major criterion and three minor criteria, or of five minor criteria. See text for further details.

[b] Transesophageal echocardiography is required for optimal assessment of possible prosthetic valve endocarditis or complicated endocarditis.

[c] Valvular disease with stenosis or regurgitation, presence of a prosthetic valve, congenital heart disease including corrected or partially corrected conditions (except isolated atrial septal defect, repaired ventricular septal defect, or closed patent ductus arteriosus), prior endocarditis, or hypertrophic cardiomyopathy.

[d] Excluding single positive cultures for coagulase-negative staphylococci and diphtheroids, which are common culture contaminants, or for organisms that do not cause endocarditis frequently, such as gram-negative bacilli.

Source: Reproduced with permission from Li JS et al: Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis* 30:633, 2000.

III-27. **The answer is E.** *(Chap. 123)* Weighing the potential benefits, potential adverse events, and costs associated with antibiotic prophylaxis, the American Heart Association and the European Society of Cardiology now recommend prophylactic antibiotics only for those patients at highest risk for severe morbidity or death from endocarditis (Table III-27). Maintaining good dental hygiene in at-risk patients is essential and a recommended goal. Prophylaxis is recommended only when there is manipulation of gingival tissue or the periapical region of the teeth or perforation of the oral mucosa (including surgery on the respiratory tract). Prophylaxis is not advised for patients undergoing gastrointestinal or genitourinary tract procedures. High-risk patients should be treated before or when they undergo procedures on an infected genitourinary tract or infected skin. The National Institute for Health and Clinical Excellence in the United Kingdom has advised discontinuation of all antibiotic prophylaxis for endocarditis. Surveillance studies have attempted to assess the impact of these new prophylaxis guidelines but have been inconclusive because of inadequate data. At best, the benefit of antibiotic prophylaxis is minimal. Most endocarditis cases do not follow a procedure. Although dental treatments have been widely considered to predispose to endocarditis, such infection occurs no more frequently in patients who are undergoing dental treatment than in matched controls who are not.

TABLE III-27 High-Risk Cardiac Lesions for Which Endocarditis Prophylaxis Is Advised Before Dental Procedures

Prosthetic heart valves
Prior endocarditis
Unrepaired cyanotic congenital heart disease, including palliative shunts or conduits
Completely repaired congenital heart defects during the 6 months after repair
Incompletely repaired congenital heart disease with residual defects adjacent to prosthetic material
Valvulopathy developing after cardiac transplantation[a]

[a] Not a target population for prophylaxis according to recommendations of the European Society for Cardiology.

Source: Table created using the guidelines published by the American Heart Association and the European Society of Cardiology (Wilson W et al: *Circulation* 116:1736, 2007 and Habib G et al: *Eur Heart J* 30:2369, 2009).

III-28. **The answer is A.** *(Chap. 123)* This patient has culture-negative endocarditis, a rare entity defined as clinical evidence of infectious endocarditis in the absence of positive blood cultures. Culture-negative endocarditis accounts for <10% of cases in all populations. In this case, evidence for subacute bacterial endocarditis includes valvular regurgitation; an aortic valve vegetation; and embolic phenomena on the extremities, spleen, and kidneys. A common reason for negative blood cultures is prior antibiotics. In the absence of this, the two most common pathogens (both of which are technically difficult to isolate in blood culture bottles) are Q fever, or *Coxiella burnetii* (typically associated with close contact with livestock), and *Bartonella*. In this case, the patient's homelessness and body louse infestation are clues for *B. quintana* infection. Diagnosis is made by blood culture about 25% of the time. Otherwise, direct polymerase chain reaction of valvular tissue, if available, or acute and convalescent serologies are diagnostic options. Empirical therapy for culture-negative endocarditis usually includes ceftriaxone and gentamicin, with or without doxycycline. For confirmed *Bartonella* endocarditis, optimal therapy is gentamicin plus doxycycline. Epstein-Barr virus and HIV do not cause endocarditis. A peripheral blood smear would not be diagnostic.

III-29. **The answer is D.** *(Chap. 123)* Although any valvular vegetation can embolize, vegetations located on the mitral valve and vegetations >10 mm are at greatest risk of embolizing. Of the choices, options C, D, and E, are large enough to increase the risk of embolization. However, only option D demonstrates the risks of both size and location. Hematogenously seeded infection from an embolized vegetation may involve any organ, but particularly affects those organs with the highest blood flow. They are seen in up to 50% of patients with endocarditis. Tricuspid lesions will lead to pulmonary septic emboli, which is common in injection drug users. Mitral and aortic lesions can lead to embolic infections in the skin, spleen, kidneys, meninges, and skeletal system. A dreaded neurologic complication is mycotic aneurysm, focal dilations of arteries at points in the arterial wall that have been weakened by infection in the vasa vasorum or septic emboli, leading to hemorrhage.

III-30. The answer is C. *(Chap. 124)* Staphylococcal scalded-skin syndrome in neonates is caused by a toxin (exfoliatin) from phage group II *Staphylococcus aureus* and leads to bullae, not vesicles. Necrotizing fasciitis and gas gangrene also induce bulla formation. Halophilic *Vibrio* infection can be as aggressive and fulminant as necrotizing fasciitis and can form bullae; a helpful clue in its diagnosis is a history of exposure to waters of the Gulf of Mexico or the Atlantic seaboard or (in a patient with cirrhosis) the ingestion of raw seafood. Meanwhile, vesicle formation due to infection may be caused by viral proliferation within the epidermis. In varicella and variola, viremia precedes the onset of a diffuse centripetal rash that progresses from macules to vesicles, not bullae, then to pustules, and finally to scabs over the course of 1–2 weeks. Vesicles of varicella have a “dewdrop” appearance and develop in crops randomly about the trunk, extremities, and face over 3–4 days.

III-31. The answer is E. *(Chap. 124)* The CT scan shows edema and inflammation of the left anterior chest wall in a patient with necrotizing fasciitis and myonecrosis consistent with infection by group A *Streptococcus*. The multiple skin excoriations were the most likely portal of entry for the bacteria. There is no evidence on the CT of lung parenchymal infection. *Actinomyces israelii*, *Klebsiella pneumoniae*, and oral anaerobic bacteria may cause necrotizing lung infections, particularly in patients with a history of alcoholism and poor dentition. *Streptococcus pneumoniae* is the most common cause of bacterial pneumonia and typically shows lobar consolidation on CT scan.

III-32. The answer is C. *(Chap. 125)* This patient has an examination concerning for septic arthritis of the knee. In patients presenting with septic arthritis, the hematogenous route of infection is the most common route in all age groups. Nearly every bacterial pathogen is capable of causing septic arthritis. Among young adults and adolescents, *Neisseria gonorrhoeae* is the most commonly implicated organism. *Staphylococcus aureus* accounts for most nongonococcal isolates in adults of all ages; gram-negative bacilli, pneumococci, and β-hemolytic streptococci—particularly groups A and B but also groups C, G, and F—are involved in up to one-third of cases in older adults, especially those with underlying comorbid illnesses. In this patient who is not sexually active, *S. aureus* would be the most likely cause. For septic arthritis, prompt administration of systemic antibiotics and drainage of the involved joint can prevent destruction of cartilage, postinfectious degenerative arthritis, joint instability, or deformity. Once samples of blood and synovial fluid have been obtained for culture, empirical IV antibiotics should be directed against the bacteria visualized on smears or the pathogens that are likely in light of the patient’s age and risk factors pending final culture results.

III-33. The answer is B. *(Chap. 126)* The patient likely has vertebral osteomyelitis. The signs and symptoms of vertebral osteomyelitis are nonspecific. Only about half of patients develop fever >38°C (>100.4°F), perhaps because patients frequently use analgesic drugs. Back pain is the leading initial symptom (>85% of cases). Neurologic deficits, such as radiculopathy, weakness, or sensory loss, are observed in about one-third of cases of vertebral osteomyelitis. Neurologic signs and symptoms are caused mostly by spinal epidural abscess. This complication starts with severe localized back pain and progresses to radicular pain, reflex changes, sensory abnormalities, motor weakness, bowel and bladder dysfunction, and paralysis. Leukocytosis and neutrophilia have low levels of diagnostic sensitivity (only 65 and 40%, respectively). In contrast, an increased erythrocyte sedimentation rate or C-reactive protein level has been reported in 98 and 100% of cases, respectively; thus, these tests are helpful in excluding vertebral osteomyelitis. The gold standard diagnostic imaging test is MRI, which should be performed expeditiously in patients with neurologic impairment to rule out a herniated disk or to detect pyogenic complications in a timely manner. Because of its low sensitivity, plain radiography generally is not helpful in acute osteomyelitis, but it can be useful in subacute or chronic cases. Understanding the cause of the vertebral osteomyelitis is essential to guide what may be an extended therapeutic course. Blood cultures are a reasonable first microbiological test. The fraction of blood cultures that yield positive results depends heavily on whether the patient has been pretreated with antibiotics; across studies, the range is from 30 to 78%. In view of this low rate of positive blood culture after antibiotic treatment, such therapy should be withheld until microbial growth is proven unless the patient has sepsis syndrome. In patients with negative blood cultures, CT-guided or open biopsy is needed.

III-34. **The answer is E.** *(Chap. 126)* The patient has symptoms and an examination consistent with chronic periprosthetic joint infection (PJI). PJI is traditionally classified as early (<3 months after implantation), delayed (3–24 months after surgery), or late (>2 years after implantation). For therapeutic decision-making, it is more useful to classify PJI as (1) acute hematogenous PJI with <3 weeks of symptoms, (2) early postinterventional PJI manifesting within 1 month after surgery, or (3) chronic PJI with symptom duration of >3 weeks. Key findings in chronic PJI are joint effusion, local pain, implant loosening, and occasionally a sinus tract. Chronic PJI is most commonly caused by low-virulence microorganisms such as coagulase-negative staphylococci or *Propionibacterium acnes*. These infections are characterized by nonspecific symptoms, such as chronic pain caused by low-grade inflammation or early loosening. Blood tests such as the measurement of C-reactive protein (elevated levels, ≥10 mg/L) and erythrocyte sedimentation rate (elevated rates, ≥30 mm/h) are sensitive (91–97%) but not specific (70–78%). Treatment of PJI requires a multidisciplinary approach involving an orthopedic surgeon and an infectious disease specialist. Therefore, most patients are referred to a specialized center. In general, the goal of treatment is cure, i.e., a pain-free functional joint with complete eradication of the infecting pathogen(s). As a rule, antimicrobial therapy without surgical intervention is not curative but merely suppressive. There are four curative surgical options: debridement and implant retention, one-stage implant exchange, two-stage implant exchange, and implant removal without replacement. To best direct treatment, in a patient who is not septic, antibiotic therapy should be deferred until joint aspiration or surgical sampling can be performed.

III-35. **The answer is A.** *(Chap. 127)* Primary (spontaneous) bacterial peritonitis (PBP) occurs when the peritoneal cavity becomes infected without an apparent source of contamination. In adults, PBP occurs most commonly in conjunction with cirrhosis of the liver (frequently the result of alcoholism). Although PBP virtually always develops in patients with pre-existing ascites, it is, in general, an uncommon event, occurring in ≤10% of cirrhotic patients. The cause of PBP has not been established definitively but is believed to involve hematogenous spread of organisms in a patient in whom a diseased liver and altered portal circulation result in a defect in the usual filtration function. Organisms multiply in ascites, a good medium for growth. The most common manifestation of PBP is fever, which is reported in up to 80% of patients. Abdominal pain, an acute onset of symptoms, and peritoneal irritation during physical examination can be helpful diagnostically, but the absence of any of these findings does not exclude this often-subtle diagnosis. Nonlocalizing symptoms (such as malaise, fatigue, or encephalopathy) without another clear etiology should also prompt consideration of PBP in a susceptible patient. It is vital to sample the peritoneal fluid of any cirrhotic patient with ascites and fever. The finding of >250 PMNs/μL is diagnostic for PBP (in this case 40% of 1000 = 400 PMNs/μL). Although enteric gram-negative bacilli such as *Escherichia coli* are most commonly encountered, gram-positive organisms such as streptococci, enterococci, or even pneumococci are sometimes found. Diagnosis is often difficult because peritoneal cultures are often negative.

III-36. **The answer is D.** *(Chap. 127)* This patient has chronic ambulatory peritoneal dialysis (CAPD)-associated peritonitis. Unlike primary or secondary bacterial peritonitis, this infection is usually caused by skin organisms, most commonly *Staphylococcus* species. The organisms migrate into the peritoneal fluid via the device. There may not be a tunnel or exit-site infection. Peritonitis is the most common reason for discontinuing CAPD.

Y-connectors and diligent technique decrease the risk of CAPD. In contrast to primary bacterial peritonitis and similar to spontaneous bacterial peritonitis (SPB), the onset of symptoms is usually acute with diffuse pain and peritoneal signs. The dialysate will be cloudy with >100 white blood cells/μL and >50% neutrophils. Dialysates should be placed in blood culture media and often are positive with one organism. Finding more than one organism in culture should prompt an evaluation for SPB. Empirical intraperitoneal coverage for CAPD peritonitis should be directed against staphylococcal species based on local epidemiology. If the patient is severely ill, IV antibiotics should be added. If the patient does not respond within 4 days, catheter removal should be considered.

III-37. The answer is D. *(Chap. 127)* The CT shows a large, complex, multiloculated liver abscess in the right lobe. Multiple or multilocular abscesses are more common than solitary abscesses. Liver abscesses may arise from biliary disease (most common currently), pylephlebitis, appendicitis with rupture, or contiguous infection in the peritoneal cavity.

Fever may be the only physical finding so liver abscess is an important cause of fever of unknown origin (FUO). Up to 50% of patients may not have localizing symptoms or signs. Diagnostic studies of the abdomen, especially the right upper quadrant, should be a part of any workup for FUO. The single most reliable laboratory finding is an elevated serum concentration of alkaline phosphatase, which is documented in 70% of patients with liver abscesses. Other tests of liver function may yield normal results, but 50% of patients have elevated serum levels of bilirubin, and 48% have elevated concentrations of aspartate aminotransferase. Other laboratory findings include leukocytosis in 77% of patients, anemia (usually normochromic, normocytic) in 50%, and hypoalbuminemia in 33%. Concomitant bacteremia is found in one-third to one-half of patients. The most common causative organisms in presumed biliary disease are gram-negative bacilli. Anaerobes are not common unless pelvic or other enteric sources are suspected. Fungal liver abscesses may occur following fungemia in immunocompromised patients receiving chemotherapy, often presenting symptomatically with neutrophil reconstitution. Drainage, usually percutaneous, is the mainstay of therapy and is useful in tailoring therapy (Figure III-37B). Antibiotic use alone without drainage seldom cures the infection.

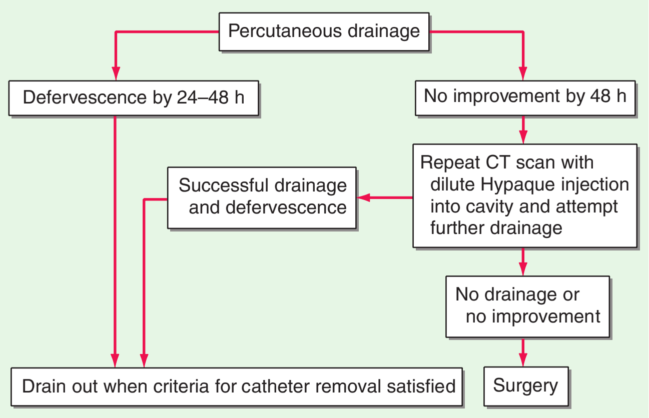

Percutaneous drainage
Defervescence by 24–48 h
No improvement by 48 h
Repeat CT scan with dilute Hypaque injection into cavity and attempt further drainage
Successful drainage and defervescence
No drainage or no improvement
Drain out when criteria for catheter removal satisfied
Surgery

FIGURE III-37B Adapted with permission from Gorbach SL et al: *Infectious Diseases*. Philadelphia: Saunders, 1992.

III-38. The answer is C. *(Chap. 128)* As well as ensuring she is up to date on routine vaccinations, she should receive or have documentation of vaccination for hepatitis A, hepatitis B, and typhoid fever. Depending on her specific travel plans, you may discuss malaria prophylaxis. You would also provide guidance on prevention of mosquito bites to prevent dengue. Meanwhile, travelers can reduce their risk of diarrhea by eating only hot, freshly cooked food; by avoiding raw vegetables, salads, and unpeeled fruit; and by drinking only boiled or treated water and avoiding ice. Historically, few travelers to tourist destinations adhere to these dietary restrictions. Bismuth subsalicylate is an inexpensive agent for the prophylaxis of traveler's diarrhea; it is taken at a dosage of 2 tablets (525 mg) four times a day. Treatment appears to be effective and safe for up to 3 weeks, but adverse events such as temporary darkening of the tongue and tinnitus can occur. A meta-analysis suggests that probiotics may lessen the likelihood of traveler's diarrhea by ~15%. Prophylactic antimicrobial agents, although effective, are not generally recommended for the prevention of traveler's diarrhea except when travelers are immunosuppressed or have other underlying illnesses that place them at high risk for morbidity from gastrointestinal infection. If prophylaxis is indicated, the nonabsorbed antibiotic rifaximin can be considered.

III-39. **The answer is A.** *(Chap. 129) Clostridium difficile* infection (CDI) is a common gastrointestinal illness that is most commonly associated with antimicrobial use and subsequent disruption of normal colonic flora. Diarrhea is the most common manifestation caused by *C. difficile*. Stools are almost never grossly bloody and range from soft and unformed to watery or mucoid in consistency, with a characteristic odor. Clinical and laboratory findings include fever in 28% of cases, abdominal pain in 22%, and leukocytosis in 50%. When adynamic ileus (which is seen on x-ray in ~20% of cases) results in cessation of stool passage, the diagnosis of CDI is frequently overlooked. A clue to the presence of unsuspected CDI in these patients is unexplained leukocytosis, with ≥15,000 white blood cells/μL. Such patients are at high risk for complications of CDI, particularly toxic megacolon, and sepsis. *C. difficile* diarrhea recurs after treatment in ~15–30% of cases. Susceptibility to recurrence of clinical CDI is likely a result of continued disruption of the normal fecal microbiota caused by the antibiotic used to treat CDI.

III-40. **The answer is D.** *(Chap. 129)* The patient has fulminant *Clostridium difficile* infection (CDI). CDI is defined as severe infection with the addition of hypotension, shock, ileus, or toxic megacolon. Indicators of severe disease may include leukocytosis (≥15,000 white blood cells [WBCs]/μL) and a creatinine level ≥1.5 times the premorbid value. Fulminant (rapidly progressive and severe) CDI presents the most difficult treatment challenge. Patients with fulminant disease often do not have diarrhea, and their illness mimics an acute surgical abdomen. Sepsis (hypotension, fever, tachycardia, leukocytosis) may result from fulminant CDI. An acute abdomen (with or without toxic megacolon) may include signs of obstruction, ileus, colon-wall thickening and ascites on abdominal CT, and peripheral-blood leukocytosis (≥20,000 WBCs/μL). Medical management of fulminant CDI is suboptimal because of the difficulty of delivering oral fidaxomicin, metronidazole, or vancomycin to the colon in the presence of ileus (Table III-40). The combination of vancomycin (given orally or via nasogastric tube and by retention enema) plus IV metronidazole has been used with some success in uncontrolled studies, as has IV tigecycline in small-scale uncontrolled studies. Surgical colectomy may be life-saving if there is no response to medical management. If possible, colectomy should be performed before the serum lactate level reaches 5 mmol/L.

III-41. **The answer is D.** (*Chap. 129,* IDSA *Clostridium difficile* guidelines 2018 https://academic.oup.com/cid/article/66/7/e1/4855916) *Clostridium difficile* infection (CDI) is diagnosed based on a combination of clinical and microbiologic criteria. Clinically, a patient with CDI is expected to have diarrhea with three or more stools per day for ≥2 days with no other recognized cause. There are a number of different tests for identifying *C. difficile* in the stool. However, no single traditional test has a high sensitivity, high specificity, and rapid turnaround. The commonly used tests for diagnosing CDI are demonstration of toxin A or B in the stool, polymerase chain reaction (PCR) or culture demonstrating presence of toxin-producing *C. difficile* in the stool, or identifying pseudomembranes in the colon on endoscopy. Most laboratory tests for toxins, including enzyme immunoassays (EIAs), lack sensitivity. However, testing of multiple additional stool specimens is not recommended. Nucleic acid amplification tests (NAATs) (including PCR) are widely used diagnostically and are both rapid and sensitive; however, concern has been raised that PCR may detect colonization with toxigenic *C. difficile* in patients who have diarrhea for a reason other than CDI. The Infectious Diseases Society of America recommends a stool toxin test as part of a multistep algorithm (i.e., glutamate dehydrogenase [GDH] plus toxin; GDH plus toxin, arbitrated by NAAT; or NAAT plus toxin) rather than a NAAT

TABLE III-40 **Recommendations for the Treatment of *Clostridium difficile* Infection**

Clinical Setting	Treatment(s)	Comments
Initial episode, mild to moderate	Oral vancomycin (125 mg qid × 10 d) ***or*** Fidaxomicin (200 mg bid × 10 d) ***or*** Oral metronidazole (500 mg tid × 10–14 d)	Oral metronidazole is less effective than the other options and may necessitate a longer treatment course for response. Metronidazole is recommended only if vancomycin or fidaxomicin is not readily accessible.
Initial episode, severe	Oral vancomycin (125 mg qid × 10 d) ***or*** Fidaxomicin (200 mg bid × 10 d)	Indicators of severe disease may include leukocytosis (≥15,000 white blood cells/μL) and a creatinine level ≥1.5 times the premorbid value.
Initial episode, fulminant	Vancomycin (500 mg PO or via nasogastric tube) plus metronidazole (500 mg IV q8h) ***plus consider*** Rectal instillation of vancomycin (500 mg in 100 mL of normal saline as a retention enema q6–8h)	Fulminant CDI is defined as severe CDI with the addition of hypotension, shock, ileus, or toxic megacolon. The duration of treatment may need to be >2 weeks and is dictated by response.
First recurrence	Oral vancomycin (125 mg qid × 10 d) ***or*** Oral vancomycin followed by a taper-and-pulse regimen,[a] ***or*** Fidaxomicin (200 mg bid × 10 d)	Treatment for the initial episode should be considered when choosing treatment for the first recurrence.
Multiple recurrences	Oral vancomycin treatment followed by a taper-and-pulse regimen ***or*** Vancomycin (125 mg qid × 10 d), then stop vancomycin and start rifaximin (400 mg bid × 2 weeks) ***or*** Fidaxomicin (200 mg bid × 10 d) ***or*** FMT	FMT has been compared to a treatment course of vancomycin and vancomycin followed by a taper-and-pulse vancomycin regimen. The true efficacy of a single FMT may be only 50–60%. It is recommended that FMT given by enema be considered only after appropriate antibiotic treatment for ≥2 recurrent CDI episodes. Other options for multiple CDI recurrences are lacking good comparative data but include: Nitazoxanide (500 mg bid × 10 d) ***or*** Vancomycin (125 mg qid × 10 d) followed by fidaxomicin (200 mg daily × 7 doses, then every other day × 13 doses)

[a] A typical taper-and-pulse vancomycin regimen following a 10-day treatment course includes 125 mg bid × 1 week, then daily × 1 week, then q2–3d for 2–8 weeks.

Abbreviations: CDI, *Clostridium difficile* infection; FMT, fecal microbiota transplantation.

alone for all specimens received in the clinical laboratory when there are no preagreed institutional criteria for patient stool submission.

III-42. **The answer is E.** (*Chap. 129, IDSA guidelines* https://academic.oup.com/cid/article/66/7/e1/4855916) Overall, ~15–30% of successfully treated patients experience recurrences of *Clostridium difficile* infection (CDI), either as relapses caused by the original organism or as reinfections following treatment. The 2018 Infectious Diseases Society of America (IDSA) *C. difficile* treatment guidelines suggest either 10 days of vancomycin or fidaxomicin is recommended over metronidazole for an initial episode of CDI. Unfortunately, as the patient was treated with metronidazole, she is at an increased risk of recurrence. She is now in the midst of her first recurrence of CDI. The 2018 IDSA *C. difficile* guidelines recommend treating a first recurrence of CDI with oral vancomycin as a tapered and pulsed regimen, or with a 10-day course of fidaxomicin, or with a 10-day course of vancomycin if metronidazole was used for the primary episode. Fecal microbiota transplantation is recommended for patients with multiple recurrences of CDI who have failed appropriate antibiotic treatments.

III-43. **The answer is E.** *(Chap. 129)* Clindamycin, ampicillin, and cephalosporins (including ceftriaxone) were the first antibiotics associated with *Clostridium difficile*–associated disease and still are. More recently, broad-spectrum fluoroquinolones, including moxifloxacin and ciprofloxacin, have been associated with outbreaks of *C. difficile*, including outbreaks in some locations of a more virulent strain that has caused severe disease among elderly outpatients. For unclear reasons, β-lactams other than the later-generation cephalosporins appear to carry a lesser risk of disease. Penicillin/β-lactamase combination antibiotics appear to have lower risk of *C. difficile*–associated disease than the other agents mentioned. Cases have even been reported associated with metronidazole and vancomycin administration. All patients initiating antibiotics should be warned to seek care if they develop diarrhea that is severe or persists, as all antibiotics carry some risk for *C. difficile*–associated disease.

III-44. The answer is E. *(Chap. 130)* Urinary tract infection (UTI) is one of the most common infections seen in primary care. The term UTI encompasses a number of clinical entities including asymptomatic bacteriuria, cystitis, pyelonephritis, and prostatitis. Acute cystitis is the most common form of UTI that is diagnosed. Except among infants and the elderly, UTI occurs far more commonly in females than in males. During the neonatal period, the incidence of UTI is slightly higher among males than among females because male infants more commonly have congenital urinary tract anomalies. After 50 years of age, obstruction from prostatic hypertrophy becomes common in men, and the incidence of UTI is almost as high among men as among women. Between 1 year and ~50 years of age, UTI and recurrent UTI are predominantly diseases of females. The prevalence of asymptomatic bacteriuria (ASB) is ~5% among women between ages 20 and 40 and may be as high as 40–50% among elderly women and men. As many as 50–80% of women in the general population acquire at least one UTI during their lifetime—uncomplicated cystitis in most cases. Recent use of a diaphragm with spermicide, frequent sexual intercourse, and a history of UTI are independent risk factors for acute cystitis. Cystitis is temporally related to recent sexual intercourse in a dose-response manner, with an increased relative risk ranging from 1.4 with one episode of intercourse in the preceding week to 4.8 with five episodes. In healthy postmenopausal women, sexual activity, diabetes mellitus, and incontinence are risk factors for UTI. In pregnant women, ASB has clinical consequences, and both screening for and treatment of this condition are indicated. Specifically, ASB during pregnancy is associated with maternal pyelonephritis, which in turn is associated with preterm delivery. Antibiotic treatment of ASB in pregnant women can reduce the risk of pyelonephritis, preterm delivery, and low-birth-weight babies.

III-45. The answer is A. *(Chap. 130)* Pyelonephritis is a symptomatic infection of the kidney. Mild cases of pyelonephritis typically present with low-grade fevers with or without lower back or costovertebral angle pain. Symptoms of severe pyelonephritis include high fevers, rigors, nausea, vomiting, and flank pain. Up to 20–30% of cases of pyelonephritis have associated bacteremia. Symptoms can presently acutely without prior symptoms of cystitis. Treatment of pyelonephritis depends on the severity of the presentation. Trimethoprim-sulfamethoxazole is not preferred in many regions of the country for empiric pyelonephritis therapy based on local resistance patterns, but it is effective for treatment of acute pyelonephritis if the organism is susceptible. Either the oral or parenteral route can be utilized with fluoroquinolones if the patient is tolerating oral therapy, and 7 days of therapy are highly effective for uncomplicated pyelonephritis. In other regions, fluoroquinolone resistance in *Escherichia coli* is quite high, but fluoroquinolones are still a preferred agent. However, given this patient's sepsis along with nausea and vomiting an IV option would be preferred in this case. Oral β-lactams are less effective than fluoroquinolones and should be used with caution. Options for parenteral therapy for uncomplicated pyelonephritis include fluoroquinolones, extended-spectrum cephalosporins with or without an aminoglycoside, or a carbapenem. Combinations of a β-lactam and a β-lactamase inhibitor (e.g., ampicillin-sulbactam, ticarcillin-clavulanate, piperacillin-tazobactam) or a carbapenem (imipenem-cilastatin, ertapenem, meropenem) can be used in patients with more complicated histories, previous episodes of pyelonephritis, anticipated antimicrobial resistance, or recent urinary tract manipulations. She does not fit any of these conditions. Therefore, an extended-spectrum cephalosporin such as ceftriaxone would be recommended for her. As she has few risk factors for antimicrobial resistance, and she is experiencing acute kidney injury, an aminoglycoside would not be recommended in this patient.

III-46. The answer is C. *(Chap. 130)* Asymptomatic bacteriuria (ASB) occurs when a patient without local or systemic symptoms of infection presents with evidence of bacteria in the urine. The diagnostic cutoff for determining ASB is $>10^5$ colony-forming units/mL. Treatment of ASB does not decrease the frequency of symptomatic infections or complications except in pregnant women, individuals undergoing urologic surgery, and perhaps neutropenic patients or those with renal transplants. In pregnant women, screening and treatment of ASB are recommended because pregnant women with untreated ASB have increased risk of preterm birth, perinatal death of the fetus, and pyelonephritis in the mother. A meta-analysis found that treating ASB in pregnant women decreased the risk of pyelonephritis by 75%.

III-47. The answer is E. *(Chap. 130)* The patient has symptoms and a history consistent with acute prostatitis. Prostatitis includes both infectious and noninfectious abnormalities of the prostate gland. Infections can be acute or chronic, are almost always bacterial in nature, and are far less common than the noninfectious entity *chronic pelvic pain syndrome* (formerly known as chronic prostatitis). Acute bacterial prostatitis presents as dysuria, frequency, and pain in the prostatic pelvic or perineal area. Fever and chills are usually present, and symptoms of bladder outlet obstruction are common. Chronic bacterial prostatitis presents more insidiously as recurrent episodes of cystitis, sometimes with associated pelvic and perineal pain. Men who present with recurrent cystitis should be evaluated for a prostatic focus as well as urinary retention.

The goal in these patients is to eradicate the prostatic infection as well as the bladder infection. A fluoroquinolone or trimethoprim-sulfamethoxazole is recommended if the uropathogen is susceptible. If acute bacterial prostatitis is suspected, antimicrobial therapy should be initiated after urine and blood are obtained for cultures. Therapy can be tailored to urine culture results and should be continued for 2–4 weeks. For documented chronic bacterial prostatitis, a 4- to 6-week course of antibiotics is often necessary. Recurrences, which are not uncommon in chronic prostatitis, often warrant a 12-week course of treatment. In this case, the best option is to choose the narrowest-spectrum effective agent, to reduce complications and prevent antibiotic resistance. In this case, the agent would trimethoprim-sulfamethoxazole.

III-48. The answer is A. *(Chap. 131)* Common causes of urethral discomfort and discharge in men include *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Mycoplasma genitalium*, *Ureaplasma urealyticum*, *Trichomonas vaginalis*, herpes simplex virus, and (rarely) adenovirus. *Gardnerella* is the usual cause of bacterial vaginosis in women and is not a pathogen in men.

III-49. The answer is C. *(Chap. 131)* The patient has symptoms consistent with urethral syndrome, characterized by "internal" dysuria with urgency and frequency and pyuria but uropathogens at counts of $\geq 10^2$/mL in urine. This is most commonly due to *Chlamydia trachomatis* or *Neisseria gonorrhoeae* and can be readily confirmed by nucleic acid amplification testing for these pathogens in the urine. "External" dysuria includes pain in the vulva during urination, often without frequency or urgency. This is found in vulvovaginal candidiasis and herpes simplex virus infection, which can be visualized on physical examination. Cervical culture would not be useful with her urinary symptoms. Elevated vaginal pH >5.0 is commonly present in trichomonal vaginitis. Clue cells on vaginal secretion microscopy suggest bacterial vaginosis.

III-50. The answer is B. *(Chap. 131)* Bacterial vaginosis is associated with *Gardnerella vaginalis* and various anaerobic and/or noncultured bacteria. Women with bacterial vaginosis generally have malodorous discharge that is white or gray. There is no external irritation; pH of vaginal fluid is usually >4.5; a fishy odor is present with 10% KOH preparation; and microscopy shows clue cells, few leukocytes, and many mixed microbiota. Normal vaginal findings are described in option D, with pH <4.5 and lactobacilli seen on microscopic examination. High pH (>4.5) with external irritation is often found in vulvovaginal candidiasis, whereas the presence of motile trichomonads is diagnostic for trichomonal vaginitis.

III-51. The answer is D. *(Chap. 131)* This patient likely has trichomonas infection. Symptomatic trichomoniasis characteristically produces a profuse, yellow, and purulent homogeneous vaginal discharge and vulvar irritation, sometimes with visible inflammation of the vaginal and vulvar epithelium and petechial lesions on the cervix (the so-called strawberry cervix, best visualized by colposcopy). The pH of vaginal fluid, normally <4.5, usually rises to ≥5. Microscopic examination of vaginal discharge mixed with saline reveals motile trichomonads in most culture-positive cases. However, saline microscopy probably detects only one-half of all cases, and, especially in the absence of symptoms or signs, culture or nucleic acid amplification test (NAAT) is usually required for detection of the organism. NAAT for *Trichomonas vaginalis* is more sensitive than culture. Treatment of asymptomatic as well as symptomatic cases reduces rates of transmission and prevents later development of symptoms.

III-52. **The answer is B.** *(Chap. 131)* Pleuritic upper abdominal pain and tenderness, usually localized to the right upper quadrant (RUQ), develops in 3–10% of women with acute pelvic inflammatory disease (PID). This perihepatitis, known as Fitz-Hugh-Curtis syndrome, arises during or after the onset of symptoms of PID and may overshadow lower abdominal symptoms, leading to a mistaken diagnosis of cholecystitis. In perhaps 5% of cases of acute salpingitis, early laparoscopy reveals perihepatic inflammation ranging from edema and erythema of the liver capsule to exudate with fibrinous adhesions between the visceral and parietal peritoneum. When treatment is delayed and laparoscopy is performed late, dense "violin-string" adhesions can be seen over the liver; chronic exertional or positional RUQ pain ensues when traction is placed on the adhesions. Although perihepatitis was for many years specifically attributed to gonococcal salpingitis, most cases are now attributed to chlamydial salpingitis. In patients with chlamydial salpingitis, serum titers of micro-immunofluorescent antibody to *Chlamydia trachomatis* are typically much higher when perihepatitis is present than when it is absent. Physical findings include RUQ tenderness and usually include adnexal tenderness and cervicitis, even in patients whose symptoms do not suggest salpingitis. Results of liver function tests and RUQ ultrasonography are nearly always normal. The presence of MPC and pelvic tenderness in a young woman with subacute pleuritic RUQ pain and normal ultrasonography of the gallbladder points to a diagnosis of perihepatitis. Peri-appendicitis (appendiceal serositis without involvement of the intestinal mucosa) has been found in ~5% of patients undergoing appendectomy for suspected appendicitis and can occur as a complication of gonococcal or chlamydial salpingitis.

III-53. **The answer is A.** *(Chap. 131)* The most common causes of genital ulceration are herpes simplex virus, syphilis, and chancroid. *Haemophilus ducreyi*, the agent responsible for chancroid, causes multiple ulcers, often starting as pustules, that are soft, friable, and exquisitely tender, as was present in this case. Gonorrhea typically manifests as a urethritis, not genital ulcers. Syphilitic ulcers (primary chancre) are firm, shallow single ulcers that are not pustular and are generally not painful. Despite these usual findings, rapid treponemal testing is indicated in all cases of genital ulceration given the disparate presentations of *Treponema pallidum*. Herpes simplex virus ulcers are quite painful but are vesicular rather than pustular. In primary infection, they may be bilateral, although with reactivation, they are generally unilateral. Primary infection with HIV usually will cause an acute febrile illness, not focal ulcers. The presence of genital ulcers increases the likelihood of acquisition and transmission of HIV.

III-54. **The answer is C.** *(Chap. 132)* This patient has encephalitis. In addition to the acute febrile illness with evidence of meningeal involvement characteristic of meningitis, the patient with encephalitis commonly has an altered level of consciousness (confusion, behavioral abnormalities), or a depressed level of consciousness ranging from mild lethargy to coma, and evidence of either focal or diffuse neurologic signs and symptoms. Patients with encephalitis may have hallucinations, agitation, personality change, behavioral disorders, and, at times, a frankly psychotic state. Focal or generalized seizures occur in many patients with encephalitis. Virtually every possible type of focal neurologic disturbance has been reported in viral encephalitis; the signs and symptoms reflect the sites of infection and inflammation. The most commonly encountered focal findings are aphasia, ataxia, upper or lower motor neuron patterns of weakness, involuntary movements (e.g., myoclonic jerks, tremor), and cranial nerve deficits (e.g., ocular palsies, facial weakness). Involvement of the hypothalamic-pituitary axis may result in temperature dysregulation, diabetes insipidus, or the development of the syndrome of inappropriate secretion of antidiuretic hormone. Despite comprehensive diagnostic efforts, the majority of cases of acute encephalitis of suspected viral etiology remain of unknown cause. Hundreds of viruses are capable of causing encephalitis, although only a limited subset is responsible for most cases in which a specific cause is identified. The most commonly identified viruses causing sporadic cases of acute encephalitis in immunocompetent adults are herpesviruses (herpes simplex virus [HSV], varicella-zoster virus [VZV], Epstein-Barr virus [EBV]). Cerebrospinal fluid (CSF) examination should be performed in all patients with suspected viral encephalitis unless contraindicated by the presence of severely increased intracranial pressure. Ideally at least 20 mL should be collected with 5–10 mL stored frozen for later studies as needed. The characteristic CSF profile of encephalitis is indistinguishable from that of viral meningitis and typically consists of a lymphocytic pleocytosis, a mildly elevated protein concentration, and a normal glucose concentration. A CSF pleocytosis (>5 cells/μL) occurs in >95% of immunocompetent patients with documented viral encephalitis. About 20% of patients with encephalitis will have a significant number of red blood cells (>500/μL) in the CSF in a nontraumatic tap. The pathologic correlate of this finding may be a hemorrhagic encephalitis of the type seen with HSV; however, CSF red blood cells occur with similar frequency and in similar numbers in patients with nonherpetic focal encephalitides.

Acyclovir is of benefit in the treatment of HSV and should be started empirically in patients with suspected viral encephalitis, especially if focal features are present, while awaiting viral diagnostic studies. Treatment should be discontinued in patients found not to have HSV encephalitis, with the possible exception of patients with severe encephalitis due to VZV or EBV.

III-55. **The answer is D.** *(Chap. 133)* When bacterial meningitis is suspected, blood cultures should be immediately obtained and empirical antimicrobial and adjunctive dexamethasone therapy initiated without delay. Bacterial meningitis is a medical emergency. The goal is to begin antibiotic therapy within 60 minutes of a patient's arrival in the emergency room. Empirical antimicrobial therapy is initiated in patients with suspected bacterial meningitis before the results of cerebrospinal fluid (CSF) Gram stain and culture are known. *Streptococcus pneumoniae* and *Neisseria meningitidis* are the most common etiologic organisms of community-acquired bacterial meningitis. Due to the emergence of penicillin- and cephalosporin-resistant *S. pneumoniae*, empirical therapy of community-acquired suspected bacterial meningitis in children and adults without risk factors for drug-resistant organisms should include a combination of dexamethasone, a third-generation cephalosporin (e.g., ceftriaxone, cefotaxime, or cefepime), and vancomycin. Acyclovir can be considered as well because herpes simplex virus encephalitis is a leading disease in the differential diagnosis, and doxycycline during tick season to treat tick-borne bacterial infections. Ceftriaxone or cefotaxime provides good coverage for susceptible *S. pneumoniae*, group B streptococci, and *Haemophilus influenzae* and adequate coverage for *N. meningitidis*. The diagnosis of bacterial meningitis is made by examination of the CSF. The need to obtain neuroimaging studies (CT or MRI) prior to lumbar puncture (LP) requires clinical judgment. In an immunocompetent patient with no known history of recent head trauma, a normal level of consciousness, and no evidence of papilledema or focal neurologic deficits, it is considered safe to perform LP without prior neuroimaging studies. If LP is delayed, empirical antibiotic therapy should be initiated after blood cultures are obtained. Antibiotic therapy initiated a few hours prior to LP will not significantly alter the CSF white blood cell count or glucose concentration, nor is it likely to prevent visualization of organisms by Gram stain or detection of bacterial nucleic acid by polymerase chain reaction assay. Ampicillin should be added to the empirical regimen for coverage of *Listeria monocytogenes* in individuals <3 months of age, those >55, or those with suspected impaired cell-mediated immunity because of chronic illness, organ transplantation, pregnancy, malignancy, or immunosuppressive therapy.

III-56. **The answer is D.** *(Chaps. 133 and 141) Streptococcus pneumoniae* is the most common cause of meningitis in adults >20 years of age, accounting for nearly half the reported cases (1.1 per 100,000 persons per year). There are a number of predisposing conditions that increase the risk of pneumococcal meningitis, the most important of which is pneumococcal pneumonia. Additional risk factors include coexisting acute or chronic pneumococcal sinusitis or otitis media, alcoholism, diabetes, splenectomy, hypogammaglobulinemia, complement deficiency, and head trauma with basilar skull fracture and cerebrospinal fluid rhinorrhea. The mortality rate remains ~20% despite antibiotic therapy. Pregnancy, age >60 years, and immunocompromised status are important risk factors for meningitis due to *Listeria monocytogenes*.

III-57. **The answer is D** *(Chap. 133)* The patient has meningococcal meningitis, as is demonstrated on her cerebrospinal fluid (CSF). Although ceftriaxone and cefotaxime provide adequate empirical coverage for *Neisseria meningitidis*, penicillin G remains the antibiotic of choice for meningococcal meningitis caused by susceptible strains. Isolates of *N. meningitidis* with moderate resistance to penicillin have been identified and are increasing in incidence worldwide. CSF isolates of *N. meningitidis* should be tested for penicillin and ampicillin susceptibility, and if resistance is found, cefotaxime or ceftriaxone should be substituted for penicillin. A 7-day course of IV antibiotic therapy is adequate for uncomplicated meningococcal meningitis. The index case and all close contacts should receive chemoprophylaxis with a 2-day regimen of rifampin (600 mg q12h for 2 days in adults and 10 mg/kg q12h for 2 days in children >1 year). Rifampin is not recommended in pregnant women. Alternatively, adults can be treated with one dose of azithromycin (500 mg) or one IM dose of ceftriaxone (250 mg). Close contacts are defined as those individuals who have had contact with oropharyngeal secretions, either through kissing or by sharing toys, beverages, or cigarettes. She is likely to have had close contact with her son and her sister, so they should receive prophylaxis. Similarly, the physician who performed her intubation without full droplet precautions should receive prophylaxis. However, the taxi driver is unlikely to have had contact with her oropharyngeal secretions through physical contact or through objects, so he does not require prophylaxis.

III-58. **The answer is D.** *(Chap. 135)* This patient has a brain abscess, which typically presents as an expanding intracranial mass lesion rather than as an infectious process. Although the evolution of signs and symptoms is extremely variable, ranging from hours to weeks or even months, most patients present to the hospital 11–12 days following onset of symptoms. The classic clinical triad of headache, fever, and a focal neurologic deficit is present in <50% of cases. The most common symptom in patients with a brain abscess is headache, occurring in >75% of patients. The headache is often characterized as a constant, dull, aching sensation, either hemicranial or generalized, and it becomes progressively more severe and refractory to therapy. Fever is present in only 50% of patients at the time of diagnosis, and its absence should not exclude the diagnosis. The new onset of focal or generalized seizure activity is a presenting sign in 15–35% of patients. Focal neurologic deficits including hemiparesis, aphasia, or visual field defects are part of the initial presentation in >60% of patients. The clinical presentation of a brain abscess depends on its location, the nature of the primary infection if present, and the level of the intracranial pressure (ICP). Hemiparesis is the most common localizing sign of a frontal lobe abscess. A temporal lobe abscess (as in this case) may present with a disturbance of language (dysphasia) or an upper homonymous quadrantanopia. Nystagmus and ataxia are signs of a cerebellar abscess. Signs of raised ICP—papilledema, nausea and vomiting, and drowsiness or confusion—can be the dominant presentation of some abscesses, particularly those in the cerebellum. Meningismus is not present unless the abscess has ruptured into the ventricle or the infection has spread to the subarachnoid space. Approximately one-third of brain abscesses are associated with otitis media and mastoiditis, as in this case, and typically lead to temporal lobe abscesses. Optimal therapy of brain abscesses involves a combination of high-dose parenteral antibiotics and neurosurgical drainage. Empirical therapy of community-acquired brain abscess in an immunocompetent patient typically includes a third- or fourth-generation cephalosporin (e.g., cefotaxime, ceftriaxone, or cefepime) and metronidazole. In patients with penetrating head trauma or recent neurosurgical procedures, treatment should include ceftazidime as the third-generation cephalosporin to enhance coverage of *Pseudomonas* spp. and vancomycin for coverage of staphylococci. Aspiration and drainage of the abscess under stereotactic guidance are beneficial for both diagnosis and therapy. Empirical antibiotic coverage should be modified based on the results of Gram stain and culture of the abscess contents. Complete excision of a bacterial abscess via craniotomy or craniectomy is generally reserved for multiloculated abscesses or those in which stereotactic aspiration is unsuccessful. Medical therapy alone is not optimal for treatment of brain abscess and should be reserved for patients whose abscesses are neurosurgically inaccessible, for patients with small (<2–3 cm) or nonencapsulated abscesses (cerebritis), and for patients whose condition is too tenuous to allow performance of a neurosurgical procedure. All patients should receive a minimum of 6–8 weeks of parenteral antibiotic therapy. In addition to surgical drainage and antibiotic therapy, patients should receive prophylactic anticonvulsant therapy because of the high risk (~35%) of focal or generalized seizures. Glucocorticoids should not be given routinely to patients with brain abscesses.

III-59. **The answer is A.** *(Chap. 136)* Antibiotics should be administered for all established bite-wound infections and should be chosen in light of the most likely potential pathogens, as indicated by the biting species and by Gram stain and culture results (Table III-59). For

TABLE III-59 Management of Wound Infections Following Animal and Human Bites

Biting Species	Commonly Isolated Pathogens	Preferred Antibiotic(s)[a]	Alternative in Penicillin-Allergic Patient	Prophylaxis Advised for Early Uninfected Wounds	Other Considerations
Dog	*Staphylococcus aureus, Pasteurella multocida,* anaerobes, *Capnocytophaga canimorsus*	Amoxicillin/clavulanate (250–500 mg PO tid) or ampicillin/sulbactam (1.5–3.0 g IV q6h)	Clindamycin (150–300 mg PO qid) plus either TMP-SMX (1 DS tablet PO bid) or ciprofloxacin (500 mg PO bid)	Sometimes[b]	Consider rabies prophylaxis.
Cat	*P. multocida, S. aureus*, anaerobes	Amoxicillin/clavulanate or ampicillin/sulbactam as above	Clindamycin plus TMP-SMX as above or a fluoroquinolone	Usually	Consider rabies prophylaxis. Carefully evaluate for joint/bone penetration.
Human, occlusional	Viridans streptococci, *S. aureus, Haemophilus influenzae*, anaerobes	Amoxicillin/clavulanate or ampicillin/sulbactam as above	Erythromycin (500 mg PO qid) or a fluoroquinolone	Always	
Human, clenched-fist	As for occlusional, plus *Eikenella corrodens*	Ampicillin/sulbactam as above or imipenem (500 mg q6h)	Cefoxitin[c]	Always	Examine for tendon, nerve, or joint involvement.
Monkey	As for human bite	As for human bite	As for human bite	Always	For macaque monkeys, consider B virus prophylaxis with acyclovir.
Snake	*Pseudomonas aeruginosa, Proteus* spp., *Bacteroides fragilis, Clostridium* spp.	Ampicillin/sulbactam as above	Clindamycin plus TMP-SMX as above or a fluoroquinolone	Sometimes, especially with venomous snakes	Administer antivenin for venomous snakebite.
Rodent	*Streptobacillus moniliformis, Leptospira* spp., *P. multocida*	Penicillin VK (500 mg PO qid)	Doxycycline (100 mg PO bid)	Sometimes	
Aquatic animal (alligator, piranha, shark, moray eel, barracuda)	*Aeromonas hydrophila,* marine *Vibrio* spp. *(Vibrio vulnificus)*	Third-generation cephalosporin (e.g., ceftriaxone, 1 g IV q24h) plus doxycycline (100 mg PO bid)	Clindamycin plus levofloxacin (750 mg PO qd) plus doxycycline	Always	Obtain prompt surgical consultation, as risk for necrotizing infection is high with *Aeromonas* and *Vibrio* spp.

[a] Antibiotic choices should be based on culture data when available. These suggestions for empirical therapy need to be tailored to individual circumstances and local conditions. IV regimens should be used for hospitalized patients. A single IV dose of antibiotics may be given to patients who will be discharged after initial management.

[b] Prophylactic antibiotics are suggested for severe or extensive wounds, facial wounds, and crush injuries; when bone or joint may be involved; and when comorbidity is present (see text).

[c] May be hazardous in patients with immediate-type hypersensitivity to penicillin.

Abbreviations: DS, double-strength; TMP-SMX, trimethoprim-sulfamethoxazole.

dog and cat bites, antibiotics should be effective against *Staphylococcus aureus, Pasteurella* sp., *Capnocytophaga canimorsus*, streptococci, and oral anaerobes. For human bites, agents with activity against *S. aureus, Haemophilus influenzae*, and β-lactamase-positive oral anaerobes should be used. The combination of an extended-spectrum penicillin with a β-lactamase inhibitor (amoxicillin/clavulanic acid, ticarcillin/clavulanic acid, ampicillin/sulbactam) appears to offer the most reliable coverage for these pathogens. Second- and third-generation cephalosporins (cefuroxime, cefoxitin, cefpodoxime) also offer substantial coverage when given in conjunction with a drug that provides anaerobic coverage. Antibiotics are generally given for 10–14 days, but the response to therapy must be carefully monitored. Failure to respond should prompt a consideration of diagnostic alternatives and surgical evaluation for possible drainage or debridement. Complications such as osteomyelitis or septic arthritis mandate a longer duration of therapy.

Bites by venomous snakes may not require antibiotic treatment. Because it is often difficult to distinguish signs of infection from tissue damage caused by the envenomation, many authorities continue to recommend treatment directed against the snake's oral flora—i.e., the administration of broadly active agents such as ceftriaxone (1–2 g IV q12–24h) or ampicillin/sulbactam (1.5–3.0 g IV q6h).

III-60. **The answer is E.** *(Chap. 137)* Nosocomial infections have reservoirs and sources just as do community-acquired pathogens. In hospitalized patients, cross-contamination (i.e., indirect spread of organisms from one patient to the next) accounts for many nosocomial infections. While hand hygiene is uniformly recommended for health care practitioners, adherence to handwashing is low, often due to time pressure, inconvenience, and skin damage. Because of improved adherence, alcohol-based hand rubs are now recommended for all health care workers except when hands are visibly soiled or after care of a patient with *Clostridium difficile* infection, whose spores may not be killed by alcohol and thus require thorough handwashing with soap and water.

III-61. **The answer is E.** *(Chap. 138)* Ultimately, solid organ transplant patients are at highest risk for infection due to T-cell immunodeficiency from anti-rejection medicines. As a result, they are also at risk for reactivation of many of the viruses from the herpes virus family, most notably cytomegalovirus, varicella-zoster virus, and Epstein-Barr virus. However, immediately after transplant, these deficits have not yet developed in full. Neutropenia is not common after solid organ transplantation, as it is in bone marrow transplantation. In fact, patients are most at risk of infections typical for all hospitalized patients, including wound infections, urinary tract infection, pneumonia, *Clostridium difficile* infection, and line-associated infection. Therefore, a standard evaluation of a febrile patient in the first weeks after a solid organ transplant should include a detailed physical examination, blood and urine cultures, urinalysis, chest radiography, *C. difficile* stool antigen/toxin studies if warranted, and a transplant-specific evaluation.

III-62. **The answer is E.** *(Chap. 138)* This patient likely has posttransplant cytomegalovirus (CMV) disease. About 50% of all renal transplant recipients presenting with fever 1–4 months after transplantation have evidence of CMV disease; CMV itself accounts for the fever in more than two-thirds of cases and thus is the predominant pathogen during this period. CMV infection may also present as arthralgias, myalgias, or organ-specific symptoms. During this period, this infection may represent primary disease (in the case of a seronegative recipient of a kidney from a seropositive donor) or may represent reactivation disease or superinfection. Patients may have atypical lymphocytosis. Unlike immunocompetent patients, however, they rarely have lymphadenopathy or splenomegaly. Therefore, clinical suspicion and laboratory confirmation are necessary for diagnosis. The clinical syndrome may be accompanied by bone marrow suppression (particularly leukopenia). CMV also causes glomerulopathy and is associated with an increased incidence of other opportunistic infections. Because of the frequency and severity of disease, a considerable effort has been made to prevent and treat CMV infection in renal transplant recipients. Ganciclovir and valganciclovir are beneficial for prophylaxis (when indicated) and for the treatment of serious CMV disease. The availability of valganciclovir has allowed most centers to move to oral prophylaxis for transplant recipients. Infection with the other herpesviruses may become evident within 6 months after transplantation or later. Early after transplantation, herpes simplex virus (prevented by valacyclovir) may cause either oral or anogenital lesions that are usually responsive to acyclovir. Large ulcerating lesions in the anogenital area may lead to bladder and rectal dysfunction and may predispose the patient to bacterial infection. Varicella-zoster virus (VZV) may cause fatal disseminated infection in nonimmune kidney transplant recipients, but in immune patients reactivation zoster usually does not disseminate outside the dermatome; thus disseminated VZV infection is a less fearsome complication in kidney transplantation. Epstein-Barr virus (EBV) disease is more serious; it may present as an extranodal proliferation of B cells that invade the central nervous system (CNS), nasopharynx, liver, small bowel, heart, and other organs, including the transplanted kidney. The disease is diagnosed by the finding of a mass of proliferating EBV-positive B cells. Disease may regress once immunocompetence is restored. Kidney transplant recipients are also subject to infections with other intracellular organisms. Pulmonary infections with *Pneumocystis* are common unless the patient is maintained on , trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis. *Nocardia* infection may present in the skin, bones, and lungs or in the CNS, where it usually takes the form of single or multiple brain abscesses. Nocardiosis generally occurs ≥1 month after transplantation and may follow immunosuppressive treatment for an episode of rejection. As it is for *Pneumocystis jirovecii* infection, prophylaxis with TMP-SMX is often efficacious in the prevention of nocardiosis.

III-63. **The answer is E.** *(Chap. 138) Toxoplasma gondii* commonly achieves latency in cysts during acute infection. Reactivation in the central nervous system in AIDS patients is well known. However, *Toxoplasma* cysts also reside in the heart. Thus, transplanting a *Toxoplasma*-positive heart into a negative recipient may cause reactivation in the months after transplant. Serologic screening of cardiac donors and recipients for *T. gondii* is important. To account for this possibility, prophylactic doses of trimethoprim-sulfamethoxazole, which is also effective prophylaxis against *Pneumocystis* and *Nocardia*, is standard after cardiac transplantation. Cardiac transplant recipients, similar to all other solid organ transplant recipients, are at risk of developing infections related to impaired cellular immunity, particularly >1 month to 1 year posttransplantation. Wound infections or mediastinitis from skin organisms may complicate the early transplant (<1 month) period.

III-64, III-65, III-66, III-67, III-68. **The answers are C, B, D, A, and E, respectively.** *(Chap. 139)* Antibacterial agents have a variety of mechanisms of action that target essential components of the bacterial cell structures and metabolism. The targets are typically chosen because they either do not exist in mammalian cells or are sufficiently different to allow for bacterial targeting. One primary target of antibacterial agents is inhibition of cell wall synthesis as mammalian cells have no counterpart to this structure. The cell wall is a cross-linked peptidoglycan that is composed of alternating units of N-acetylglucosamine (NAG) and N-acetylmuramic acid (NAM). Inhibition of this peptidoglycan synthesis is a target of many antibacterial agents and leads to cell lysis, making these antibiotics bactericidal in nature. Antibacterial drugs that inhibit cell wall synthesis include β-lactams, glycopeptides, bacitracin, and fosfomycin. β-Lactams are a large category of drugs that include penicillins, carbapenems, cephalosporins, and monobactams. All of these agents contain a β-lactam ring that targets transpeptidase enzymes (also called penicillin-binding proteins) to inhibit peptide cross-linking in the formation of peptidoglycan. Glycopeptides bind to the glycosyltransferase enzyme that polymerizes NAG-NAM units. Antibiotics in this class include vancomycin, telavancin, dalbavancin, and oritavancin. Bacitracin and fosfomycin act early in peptidoglycan synthesis to decrease production of the peptidoglycan precursors. Inhibition of bacterial protein synthesis is also a common target of antibacterial drugs. These drugs bind within the bacterial ribosome and are most commonly bacteriostatic, although aminoglycoside antibiotics are bactericidal. Examples of antibacterial drugs that inhibit protein synthesis are aminoglycosides, tetracyclines, macrolides, lincosamides, streptogramins (quinupristin-dalfopristin), chloramphenicol, oxazolidinones (linezolid and tedizolid), and mupirocin. Aminoglycosides bind irreversibly to the 16S ribosomal RNA of the 30S ribosomal subunit to prevent protein synthesis. This class of medication can also cause misreading of the messenger RNA codon. Tobramycin, gentamicin, and amikacin are commonly used aminoglycosides. Tetracyclines also bind to the 16S ribosomal RNA of the 30S ribosomal subunit, but, in contrast to aminoglycosides, the binding is reversible. Most of the other inhibitors of protein synthesis bind at the 23S ribosomal RNA of the 50S subunit, but all have slightly different mechanisms of inhibition at the site. Mupirocin is only available topically and directly inhibits production of tRNA synthetase. Folate is a required cofactor in the synthesis of some nucleic acids and amino acids. Sulfonamides prevent folate synthesis by inhibiting enzymes within cells that use exogenous precursors to generate folate. Trimethoprim is also a folate synthesis inhibitor that acts farther down the pathway of folate synthesis. When trimethoprim is used in combination with sulfamethoxazole, two subsequent steps in folate synthesis are inhibited. There are also multiple classes of antibiotics that inhibit DNA or RNA synthesis. The most commonly used class of these drugs is the fluoroquinolones, which inhibit DNA gyrase and topoisomerase IV. Rifamycins bind to bacterial RNA polymerase and prevent elongation of mRNA. Nitrofurantoin metabolism within the cell leads to reactive derivatives that cause DNA strand breakage. Metronidazole also creates reactive species that damage DNA and lead to cell death. Finally, two classes of agents act directly to disrupt the integrity of the bacterial cytoplasmic membrane. Polymyxins, including colistin, and daptomycin are the available agents in the class.

III-69. The answer is C. *(Chap. 139)* Pharmacokinetics and pharmacodynamics both play important roles in understanding the appropriate use of antibiotics. Pharmacokinetics refers to the disposition of a drug in the body and includes the absorption, distribution, metabolism, and excretion of the drug. IV use of a drug leads to 100% of absorption of a drug. Other routes of drug administration yield varying degrees of bioavailability and are subject to first-pass effects. Once a drug is in the body, distribution refers to how the drug is passed between the circulation and tissues, and it is important to consider the volume of distribution of a drug. This refers to the amount of drug in the body at a given time relative to the measured serum concentration. Patients with cystic fibrosis are known to have a higher volume of distribution of medications with more rapid drug clearance. Thus, higher doses of antibiotics are often required. Some medications require therapeutic drug monitoring to determine whether appropriate drugs levels are attained to achieve effective killing while minimizing side effects. It is important to consider drug metabolism and excretion when determining the appropriate time to assess drug levels. Generally, five to seven half-lives of the drug are required for levels to achieve steady state when multiple doses of a medication are given in a time frame shorter than the half-life itself. Trough levels prior to drug administration are performed to ensure that the drug is not accumulating and to prevent side effects. Pharmacodynamics describes the relationship between the serum concentration that achieves the desired drug effect and the serum concentration that can produce toxic effects of the drug. When considering the pharmacodynamics of an antibiotic, it is important to consider whether the drug achieves efficacy through time- or concentration-dependent killing. β-Lactams are an example of a drug that kills in a time-dependent fashion. Thus, these agents do not require high peak levels for efficacy; rather, the important factor in achieving effect is to determine the length of time the drug will be maintained at concentrations greater than the minimal inhibitory concentration (MIC). The longer the concentration of a β-lactam remains above the MIC during the dosing interval, the greater is the killing effect, and using prolonged infusions of β-lactams has been used as a way to improve time-dependent killing. In contrast, concentration-dependent killing requires higher peak concentration of a drug to achieve the desired effect. Aminoglycosides are antibiotics that use concentration-dependent pharmacodynamics.

III-70. The answer is D. *(Chap. 139)* Pregnancy affects decisions regarding antibacterial therapy in two respects. First, pregnancy is associated with an increased risk of particular infections (e.g., those caused by *Listeria*). Second, the potential risks to the fetus that are posed by specific drugs must be considered (Table III-70). As for other drugs, the safety of the vast majority of antibacterial agents in pregnancy has not been established, and such agents are grouped in categories B and C by the U.S. Food and Drug Administration. Drugs in

TABLE III-70 Risks Associated with Use of Antibacterial Drugs in Pregnancy and Lactation

Pregnancy Category[a]	Antibacterial Drug	Fetal Risk Recommendation[b]	Breastfeeding Risk Recommendation[b]
B	Azithromycin	Limited human data. Animal data suggest low risk.	Limited human data; probably compatible.
	Cephalosporins (including cephalexin, cefuroxime, cefixime, cefpodoxime, cefotaxime, and ceftriaxone)	Compatible	Compatible
	Ceftazidime-avibactam	No human data; no fetal harm in animal studies	Ceftazidime is excreted into human milk in low concentrations. Avibactam is excreted into the milk of lactating rats; no human studies have been conducted.
	Ceftolozane-tazobactam	Compatible	Unknown
	Clindamycin	Compatible	Compatible
	Ertapenem	No human data; probably compatible	Limited human data; probably compatible
	Erythromycin	Compatible (except for estolate salt)	Compatible
	Meropenem and meropenem-vaborbactam	No human data. Animal data suggest low risk.	No human data; probably compatible
	Metronidazole	Human data suggest low risk.	Interrupt breastfeeding for 12–24 h after single 2-g dose. Limited human data; potential toxicity in divided doses
	Nitrofurantoin	Human data suggest risk in third trimester.	Limited human data; probably compatible. Higher risk associated with younger infants and those with G6PD deficiency.
	Penicillins (including amoxicillin, ampicillin, and cloxacillin)	Compatible	Compatible
	Quinupristin-dalfopristin	Compatible. Maternal benefit must far outweigh risk to embryo/fetus.	No human data; potential toxicity
	Vancomycin	Compatible	Limited human data; probably compatible
C	Chloramphenicol	Compatible	Limited human data; potential toxicity
	Fluoroquinolones	Human data suggest low risk.	Limited human data; probably compatible
	Clarithromycin	Limited human data. Animal data suggest high risk.	No human data; probably compatible
	Imipenem-cilastatin	Limited human data. Animal data suggest low risk.	Limited human data; probably compatible
	Linezolid	Compatible. Maternal benefit must far outweigh risk to embryo/fetus.	No human data; potential toxicity
	Telavancin	No human data. Animal studies have revealed evidence of teratogenicity.[c]	No human data. Animal studies have revealed evidence of teratogenicity.[c]
	Tedizolid	Limited data. Embryo-fetal studies in mice, rats, and rabbits have demonstrated fetal developmental toxicities. Use only if benefit outweighs risk.	Excreted in the breast milk of rats; unknown in humans; caution use
	Dalbavancin	Limited human data. At high doses in animal studies, delayed fetal maturation, increased embryo and offspring death. Use only if benefit outweighs risk.	Excreted in the breast milk of animals; unknown in humans; caution use
	Oritavancin	Limited human data. Studies in rats and rabbits demonstrated no harm at 25% of recommended human dose. Use only if benefit outweighs risk.	Excreted in the breast milk of rats; unknown in humans; caution use
C/D	Amikacin	Human data suggest low risk.	Compatible
	Gentamicin	Human data suggest low risk.	Compatible

(*continued*)

TABLE III-70 Risks Associated with Use of Antibacterial Drugs in Pregnancy and Lactation (*Continued*)

Pregnancy Category[a]	Antibacterial Drug	Fetal Risk Recommendation[b]	Breastfeeding Risk Recommendation[b]
D	Kanamycin	Human data suggest risk.	Limited human data; probably compatible
	Streptomycin	Human data suggest risk.	Compatible
	Sulfonamides	Human data suggest risk in third trimester.	Limited human data; potential toxicity. Avoid in ill, stressed, premature infants and in infants with hyperbilirubinemia or G6PD deficiency.
	Tetracyclines	Contraindicated in second and third trimesters	Compatible
	Tigecycline	Human data suggest risk in second and third trimesters.	No human data; potential toxicity

[a] *Category B: Either* animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women, *or* animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester. *Category C:* Animal reproduction studies have shown an adverse effect on the fetus, and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. *Category D:* There is positive evidence of human fetal risk based on adverse-reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

[b] Fetal risk recommendation and breastfeeding risk recommendation adapted from GG Briggs et al (eds.): *Drugs in Pregnancy and Lactation*, 9th ed. Philadelphia: Lippincott Williams and Wilkins, 2011; and the U.S. Food and Drug Administration (Drugs@FDA). A registry has been established to monitor pregnancy outcomes of pregnant women exposed to telavancin. Physicians are encouraged to register pregnant patients, or pregnant women may enroll themselves by calling 1-855-633-8479.

Abbreviation: G6PD, glucose-6-phosphate dehydrogenase.

categories D and X are contraindicated in pregnancy or lactation due to established risks. The safest class of drugs is class A, which indicates that studies have demonstrated safety of the drug without effects on the fetus. No antibiotic is designated as a class A drug in pregnancy. Class B drugs show no effects in animal reproduction, or if the animal data show effects, there are adequate data in pregnant women to show these drugs can be safely used. Many antibiotics fall into class B drugs in pregnancy, including azithromycin, cephalosporins, clindamycin, meropenem, penicillins, and vancomycin. Class C drugs have more potential risks, but one has to determine whether the potential benefits to the health of the mother warrant use despite the potential risk. Antibiotics in this category include fluoroquinolones and linezolid. Class D drugs demonstrate some degree of fetal risk and should be avoided if other safer alternatives exist. Sulfonamides and tetracyclines are class D drugs. The specific concern for use of doxycycline in the second and third trimester is discoloration of the teeth in the fetus.

III-71. **The answer is D.** *(Chap. 139)* All antibiotics have adverse effects that need to be considered when prescribing a drug. The most common serious side effect of all antibiotic medications is the development of drug allergy, with rash, hives, anaphylaxis or Stevens-Johnson syndrome. Some antibiotics have very specific associated syndromes. Prolonged use of nitrofurantoin is associated with development of pulmonary fibrosis and/or pneumonitis. No other antibiotic has this associated side effect. Cephalosporins and other β-lactams frequently cause hypersensitivity reactions, including anaphylaxis. Fluoroquinolones characteristically are associated with tendinitis. They may also cause dysglycemia, a side effect that caused the withdrawal of one fluoroquinolone (gatifloxacin) from the market.

Trimethoprim-sulfamethoxazole is commonly associated with a rash. Prolonged use can lead to nephrotoxicity, and patients commonly develop evidence of a type IV renal tubular acidosis. Other antibiotics with distinct clinical side effect profiles include red-man syndrome with vancomycin infusions, myopathy with daptomycin, myelosuppression with linezolid, and orange discoloration of body fluids with rifampin.

III-72. and III-73. **The answers are D and D, respectively.** *(Chap. 140)* Bacteria have a variety of methods to develop resistance to antibacterial therapy. These broadly fall into three categories: (1) altered targets that have reduced binding of the drug; (2) altered access of the drug to its target through decreased uptake or increased active efflux, and (3) a modification of the drug that reduces its activity. For β-lactam antibiotics, the most common mechanism of resistance is for the drugs to be degraded by β-lactamases, enzymes that break down the β-lactam ring and thus destroy drug activity. β-Lactamases may be encoded on the bacterial chromosome, which would affect the susceptibility profile of an entire species of bacteria. Others are acquired through plasmids, and thus, some strains may show susceptibility to a β-lactam, whereas others may not. Most strains of *Staphylococcus aureus* produce a plasmid-encoded β-lactamase that degrades penicillin, but not semisynthetic penicillins such as oxacillin and nafcillin. β-Lactamases acquired by gram-negative bacteria are encoded on plasmids and cause these bacteria to be resistant to penicillins and all early-generation cephalosporins. Most recently, an extended-spectrum β-lactamase (ESBL) has been identified, initially in *Klebsiella* species, but has not been seen in other gram-negative organisms. Presence of an ESBL identifies bacteria that will have resistance to all early (cefazolin) and later-generation cephalosporins (e.g., cefepime, ceftriaxone, ceftazidime), as well as aztreonam. Carbapenems such as meropenem are the drugs of choice to treat an ESBL-producing bacteria.

III-74. **The answer is A.** *(Chap. 141)* Pneumococcal infections, particularly pneumonia, remain a worldwide public health problem. Intermittent colonization of the nasopharynx by pneumococcus transmitted by respiratory droplet is common and is the likely reservoir for invasive disease. Infants and elderly are at greatest risk of developing invasive pneumococcal disease (IPD) and death. In the developed world, children are the most common source of pneumococcal transmission. By 1 year old, 50% of children have had at least one episode of colonization. Prevalence studies show carriage rates of 20–50% in children up to 5 years old and up to 15% for adults. These numbers approach 90% for children and 40% for adults in the developing world. Pneumococcal vaccination has dramatically impacted the epidemiology, with reduced IPD in the United States attributable to reductions in serotypes included in the vaccine. Similar reductions have been observed in other countries implementing routine childhood vaccinations; however, in certain populations (Alaska native populations and the United Kingdom), the reduction in vaccine-covered serotype cases has been offset by increases in nonvaccine serotypes. Case fatality rates due to pneumococcal pneumonia vary by host factors, age, and access to care. Interestingly, there appears to be no reduction in case fatality during the first 24 hours of hospitalization since the introduction of antibiotics. This is likely due to the development of severe multiorgan failure as a result of severe infection. Appropriate care in an intensive care setting can reduce case fatality rate for severe infection. Outbreaks of disease are well recognized in crowded settings with susceptible individuals, such as infant daycare facilities, military barracks, and nursing homes. Furthermore, there is a clear association between preceding viral respiratory disease (especially but not exclusively influenza) and risk of secondary pneumococcal infections. The significant role of pneumococcal pneumonia in the morbidity and mortality associated with seasonal and pandemic influenza is increasingly recognized.

III-75. **The answer is D.** *(Chap. 141)* The characteristics described are unique to the pneumococcus, or *Streptococcus pneumoniae*. Pneumococci are spherical gram-positive bacteria of the genus *Streptococcus*. Within this genus, cell division occurs along a single axis, and bacteria grow in chains or pairs, hence the name *Streptococcus*, from the Greek *streptos*, meaning "twisted," and *kokkos*, meaning "berry." At least 22 streptococcal species are recognized and are divided further into groups based on their hemolytic properties. *S. pneumoniae* belongs to the α-hemolytic group that characteristically produces a greenish color on blood agar because of the reduction of iron in hemoglobin. The bacteria are fastidious and grow best in 5% CO_2 but require a source of catalase (e.g., blood) for growth on agar plates, where they develop mucoid (smooth/shiny) colonies. Pneumococci without a capsule produce colonies with a rough surface. Unlike that of other α-hemolytic streptococci, their growth is inhibited in the presence of optochin (ethylhydrocupreine hydrochloride), and they are bile soluble. In common with other gram-positive bacteria, pneumococci have a cell membrane beneath a cell wall, which in turn is covered by a polysaccharide capsule. Pneumococci are divided into serogroups or serotypes based on capsular polysaccharide structure, as distinguished with rabbit polyclonal antisera; capsules swell in the presence of specific antiserum (the quellung reaction). The staphylococcal organisms grow not in chains, but in clusters. *S. pyogenes* exhibit a β-hemolytic pattern (complete hemolysis). *Pseudomonas* is gram negative.

III-76. The answer is E. *(Chap. 141)* The radiographic appearance of pneumococcal pneumonia is varied; it classically consists of lobar or segmental consolidation but in some cases is patchy. More than one lobe is involved in ~30% of cases. Blood drawn from patients with suspected pneumococcal pneumonia can be used for supportive or definitive diagnostic tests. Blood cultures are positive for pneumococci in a minority (<30%) of cases of pneumococcal pneumonia, as evidenced especially by vaccine clinical trials, which provide an independent method to reveal the contribution of the pneumococcus to pneumonia cases. Urinary pneumococcal antigen assays have facilitated etiologic diagnosis, but the application of the results is confounded by the fact that nasopharyngeal colonization with the pneumococcus, in the absence of disease, also results in a positive test. In adults, therefore, a positive pneumococcal urinary antigen test has a high predictive value for etiologic attribution of pneumonia because the prevalence of pneumococcal nasopharyngeal colonization is relatively low. Most cases of pneumococcal pneumonia in adults are diagnosed by Gram staining and culture of sputum. The utility of a sputum specimen is directly related to its quality and the patient's antibiotic treatment status. Empyema is the most common focal complication of pneumococcal pneumonia, occurring in <5% of cases. When fluid in the pleural space is accompanied by fever and leukocytosis (even low-grade) after 4–5 days of appropriate antibiotic treatment for pneumococcal pneumonia, empyema should be considered. Parapneumonic effusions are more common than empyema, representing a self-limited inflammatory response to pneumonia.

III-77. The answer is A. *(Chap. 141)* Penicillin-resistant pneumococci were first described in the mid-1960s, at which point tetracycline- and macrolide-resistant strains had already been reported. Multidrug-resistant strains were first described in the 1970s, but it was during the 1990s that pneumococcal drug resistance reached pandemic proportions. The use of antibiotics selects for resistant pneumococci, and strains resistant to β-lactam agents and to multiple drugs are now found all over the world. The emergence of high rates of macrolide and fluoroquinolone resistance also has been described. As a result of the increased prevalence of resistant pneumococci, first-line therapy for persons ≥1 month of age is a combination of vancomycin (adults, 30–60 mg/kg per day; infants and children, 60 mg/kg per day) and cefotaxime (adults, 8–12 g/d in 4–6 divided doses; children, 225–300 mg/kg per day in 1 dose or 2 divided doses) or ceftriaxone (adults, 4 g/d in 1 dose or 2 divided doses; children, 10 mg/kg per day in 1 dose or 2 divided doses). If children are hypersensitive to β-lactam agents (penicillins and cephalosporins), rifampin (adults, 600 mg/d; children, 20 mg/d in 1 dose or 2 divided doses) can be substituted for cefotaxime or ceftriaxone. For outpatient management, amoxicillin (1 g q8h) provides effective treatment for virtually all cases of pneumococcal pneumonia. Neither cephalosporins nor quinolones, which have far more side effects, offer any advantage over amoxicillin. Levofloxacin (500–750 mg/d as a single dose) and moxifloxacin (400 mg/d as a single dose) also are highly likely to be effective in the United States, except in patients who come from populations where these drugs are used widely or who have themselves been treated recently with a quinolone. Clindamycin (600–1200 mg/d q6h) is effective in 90% of cases, and azithromycin (500 mg on day 1 followed by 250–500 mg/d) or clarithromycin (500–750 mg/d as a single dose) is ineffective in 80% of cases. Treatment failure resulting in bacteremic disease due to macrolide-resistant isolates has been amply documented in patients given azithromycin empirically.

III-78. The answer is C. *(Chap. 142)* The micrograph shows gram-positive round (cocci) bacteria growing in clumps. *Haemophilus influenzae* is a gram-negative coccus, and *Pseudomonas* is a gram-negative bacillus (rod). Streptococcal species grow in chains or pairs and do not produce catalase. *Staphylococcus aureus* distinguishes itself from other staphylococcal species, including *S. epidermidis*, by the production of coagulase. Community-acquired respiratory tract infections due to *S. aureus* often follow viral infections—most commonly influenza. Patients may present with fever, bloody sputum production, and midlung-field pneumatoceles or multiple, patchy pulmonary infiltrates. Diagnosis is made by sputum Gram stain and culture. Blood cultures, although useful, are usually negative.

III-79. The answer is C. *(Chap. 142) Staphylococcus aureus* is both a commensal and an opportunistic pathogen. Approximately 30% of healthy persons are episodically colonized with *S. aureus*, with a smaller percentage (~10%) persistently colonized. The rate of colonization is elevated among insulin-dependent diabetics, HIV-infected patients, patients undergoing hemodialysis, injection drug users, and individuals with skin damage. The anterior nares and oropharynx are frequent sites of human colonization, although the skin (especially when damaged), vagina, axilla, and perineum may also be colonized. These colonization sites serve as a reservoir for future infections. Transmission of *S. aureus* most frequently results from direct personal contact. Colonization of different body sites allows transfer from one person to another during contact. Spread of staphylococci in aerosols of respiratory or nasal secretions from heavily colonized individuals has also been reported. Most individuals who develop *S. aureus* infections become infected with a strain that is already a part of their own commensal flora. Breaches of the skin or mucosal membrane allow *S. aureus* to initiate infection. Some diseases increase the risk of *S. aureus* infection; diabetes, for example, combines an increased rate of colonization and the use of injectable insulin with the possibility of impaired leukocyte function. Individuals with congenital or acquired qualitative or quantitative defects of polymorphonuclear leukocytes are at increased risk of *S. aureus* infections; this group includes neutropenic patients (e.g., those receiving chemotherapeutic agents), those with chronic granulomatous disease, and those with Job or Chédiak-Higashi syndrome. Other groups at risk include individuals with end-stage renal disease, HIV infection, skin abnormalities, or prosthetic devices.

III-80. The answer is E. *(Chap. 142) Staphylococcus aureus* produces three types of toxin: cytotoxins, pyrogenic toxin superantigens, and exfoliative toxins. Toxic shock syndrome (TSS) results from the ability of enterotoxins and TSS toxin-1 to function as T-cell mitogens. In the normal process of antigen presentation, the antigen is first processed within the cell, and peptides are then presented in the major histocompatibility complex (MHC) class II groove, initiating a measured T-cell response. In contrast, enterotoxins bind directly to the invariant region of MHC—outside the MHC class II groove. The enterotoxins can then bind T-cell receptors via the vβ chain; this binding results in a dramatic overexpansion of T-cell clones (up to 20% of the total T-cell population). The consequence of this T-cell expansion is a "cytokine storm," with the release of inflammatory mediators that include interferon-γ, interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)-α, and TNF-β. The resulting multisystem disease produces a constellation of findings that mimic those in endotoxin shock; however, the pathogenic mechanisms differ. For TSS, investigators recommend a combination of clindamycin and a semisynthetic penicillin or vancomycin (if the isolate is resistant to methicillin). Clindamycin is advocated because, as a protein synthesis inhibitor, it reduces toxin synthesis in vitro. Linezolid also appears to be effective. In most cases of staphylococcal TSS (including nonmenstrual cases), a skin site of infection is not clinically apparent. Because this disease is mediated by toxin formation, blood cultures are almost always negative. Desquamation of the skin often occurs 1–2 weeks after the onset of the illness. Staphylococcal scalded skin syndrome, which affects primarily newborns and children, exhibits skin desquamation very early in the disease.

III-81. The answer is B. *(Chap. 142)* The blood cultures that are positive for Gram-positive cocci in clusters and the overall clinical presentation are most consistent with right-sided *Staphylococcus aureus* endocarditis. The CT is consistent with septic emboli to the lung. *S. aureus* bacteremia may be complicated by sepsis, endocarditis, vasculitis, or metastatic seeding (establishment of suppurative collections at other tissue sites). Among the more commonly seeded tissue sites are bones, joints, kidneys, and lungs. The frequency of metastatic seeding during bacteremia has been estimated to be as high as 31%. The incidence of complications increases with the duration of the bacteremia. Recognition of these complications by clinical and laboratory diagnostic methods alone is often difficult. Comorbid conditions that are frequently seen in association with *S. aureus* bacteremia and that increase the risk of complications include diabetes, HIV infection, and renal insufficiency. Other host factors associated with an increased risk of complications include presentation with community-acquired *S. aureus* bacteremia (except in injection drug users), lack of an identifiable primary focus of infection, and the presence of prosthetic devices or material. The overall incidence of *S. aureus* endocarditis has increased over the past 20 years.

S. aureus is now the leading cause of endocarditis worldwide, accounting for 25–35% of cases. This increase is due, at least in part, to the increased use of intravascular devices. Studies using transesophageal echocardiography found an endocarditis incidence of ~25% among patients with intravascular catheter–associated *S. aureus* bacteremia. Other factors associated with an increased risk of endocarditis are injection drug use, hemodialysis, the presence of intravascular prosthetic devices at the time of bacteremia, and immunosuppression. Patients with implantable cardiac devices (e.g., permanent pacemakers) are at increased risk of endocarditis or device-related infections. Despite the availability of effective antibiotics, mortality rates from these infections continue to range from 20 to 40%, depending on both the host and the nature of the infection. Complications of *S. aureus* endocarditis include cardiac valvular insufficiency, peripheral emboli, metastatic seeding, vasculitis, and central nervous system involvement (e.g., mycotic aneurysms, embolic strokes). *S. aureus* endocarditis is encountered in four clinical settings: (1) right-sided endocarditis in association with injection drug use, (2) left-sided native-valve endocarditis, (3) prosthetic-valve endocarditis, and (4) nosocomial endocarditis. In each of these settings, the diagnosis is suspected from the patient's history and the recognition of clinical stigmata suggestive of endocarditis. These findings include cardiac manifestations, such as new or changing cardiac valvular murmurs; cutaneous evidence, such as vasculitic lesions, Osler nodes, or Janeway lesions; evidence of right- or left-sided embolic disease; and a history suggesting a risk for *S. aureus* bacteremia. In the absence of antecedent antibiotic therapy, blood cultures are almost uniformly positive. Transthoracic echocardiography, while less sensitive than transesophageal echocardiography, is less invasive and identifies valvular vegetations. Acute right-sided tricuspid valvular *S. aureus* endocarditis is most often seen in injection drug users. The classic presentation includes a high fever, a toxic clinical appearance, pleuritic chest pain, and the production of purulent (sometimes bloody) sputum. Chest x-rays or CT scans reveal evidence of septic pulmonary emboli (small, peripheral, circular lesions that may cavitate with time). A high percentage of affected patients have no history of antecedent valvular damage. At the outset of their illness, patients may present with fever alone, without cardiac or other localizing findings. As a result, a high index of clinical suspicion is essential for diagnosis.

III-82. The answer is E. *(Chap. 142)* Probably because of their ubiquity and ability to stick to foreign surfaces, coagulase-negative *Staphylococcus* species such as *S. epidermidis* are the most common cause of infections of central nervous system shunts as well as an important cause of infections on artificial heart valves and orthopedic prostheses. *Corynebacterium* spp. (diphtheroids), just like coagulase-negative *Staphylococcus* species, colonize the skin. When these organisms are isolated from cultures of shunts, it is often difficult to be sure if they are the cause of disease or simply contaminants. Leukocytosis in cerebrospinal fluid, consistent isolation of the same organism, and the character of a patient's symptoms are all helpful in deciding whether treatment for infection is indicated.

III-83. The answer is E. *(Chap. 142) Staphylococcus aureus* is both a commensal and an opportunistic pathogen. The rate of colonization is elevated among insulin-dependent diabetics, HIV-infected patients, patients undergoing hemodialysis, injection drug users, and individuals with skin damage. The anterior nares and oropharynx are frequent sites of human colonization, although the skin (especially when damaged), vagina, axilla, and perineum are also often colonized. These colonization sites serve as potential reservoirs for future infections.

III-84. The answer is B. *(Chap. 143)* She has erysipelas, caused by group A streptococcal infection of the superficial dermis. Erysipelas, is characterized by a bright red appearance of the involved skin, which forms a plaque that plateaus and is sharply demarcated from surrounding normal skin. The lesion is warm to the touch, may be tender, and appears shiny and swollen. The skin often has a *peau d'orange* texture, which is thought to reflect involvement of superficial lymphatics; superficial blebs or bullae may form, usually 2–3 days after onset. The lesion typically develops over a few hours and is associated with fever and chills. Erysipelas tends to occur on the malar area of the face (often with extension over the bridge of the nose to the contralateral malar region) or on the lower extremities.

After one episode, recurrence at the same site—sometimes years later—is not uncommon. Classic cases of erysipelas, with typical features, are almost always due to β-hemolytic streptococci, usually group A and occasionally group C or G. First-line therapy for all group A streptococcal infections includes IV penicillin G.

III-85. **The answer is E.** *(Chap. 143)* Necrotizing fasciitis (hemolytic streptococcal gangrene) involves the superficial and/or deep fascia investing the muscles of an extremity or the trunk. The source of the infection is either the skin, with organisms introduced into tissue through trauma (sometimes trivial), or the bowel flora, with organisms released during abdominal surgery or from an occult enteric source, such as a diverticular or appendiceal abscess. The inoculation site may not be apparent and is often some distance from the site of clinical involvement; e.g., the introduction of organisms via minor trauma to the hand may be associated with clinical infection of the tissues overlying the shoulder or chest. Cases associated with the bowel flora are usually polymicrobial, involving a mixture of anaerobic bacteria (such as *Bacteroides fragilis* or anaerobic streptococci) and facultative organisms (usually gram-negative bacilli). Cases unrelated to contamination from bowel organisms are most commonly caused by group A streptococci (GAS) alone or in combination with other organisms (most often *Staphylococcus aureus*). Overall, GAS is implicated in ~60% of cases of necrotizing fasciitis. The onset of symptoms is usually quite acute and is marked by severe pain at the site of involvement, malaise, fever, chills, and a toxic appearance. The physical findings, particularly early on, may not be striking, with only minimal erythema of the overlying skin. Pain and tenderness are usually severe. In contrast, in more superficial cellulitis, the skin appearance is more abnormal, but pain and tenderness are only mild or moderate. As the infection progresses (often over several hours), the severity and extent of symptoms worsen, and skin changes become more evident, with the appearance of dusky or mottled erythema and edema. The marked tenderness of the involved area may evolve into anesthesia as the spreading inflammatory process produces infarction of cutaneous nerves. *Streptococcus pneumoniae* and *S. epidermidis* are not causes of necrotizing fasciitis. *Clostridium difficile* causes antibiotic-associated colitis.

III-86. **The answer is E.** (*Chap. 143, Am Fam Physician* 94:24, 2016) Most cases of pharyngitis are caused by viruses—about 85–95% in adults and children under age 5 and about 70% in children aged 5–15. The most common bacterial cause of pharyngitis is group A streptococcus (GAS). Bacterial pharyngitis generally does not present with rhinorrhea, cough, or conjunctivitis and GAS is the only cause of pharyngitis for which antibiotics are indicated. The Centor criteria are important in helping decide whether a patient is likely to have streptococcal pharyngitis. Centor criteria are composed of four findings: fever, tonsillar exudate or swelling, tender anterior cervical lymphadenopathy, and absence of cough. The probability of GAS pharyngitis increases as more criteria are met. This patient has tonsillar exudate; however he has no other criteria. He only meets one criteria for GAS pharyngitis. For patients who meet zero or just one criterion, the probability of GAS pharyngitis is so unlikely that you can rule it out as the etiology of your patient's symptoms without even performing a rapid GAS test. If your patient fulfills two or three criteria, the probability of GAS pharyngitis is increased and a rapid GAS test can be performed to help confirm your clinical findings. If your patient meets all four criteria, the probability of GAS pharyngitis is high enough that you may either perform a rapid GAS test to confirm or simply clinically diagnose and treat for GAS without testing. The sensitivity of rapid tests for GAS is >90%.

III-87. **The answer is B.** *(Chap. 143)* Because the usual source of the organisms infecting a neonate is the mother's birth canal, efforts have been made to prevent group B streptococcal infections by the identification of high-risk carrier mothers and treatment with various forms of antibiotic prophylaxis or immunoprophylaxis. Prophylactic administration of ampicillin or penicillin to such patients during delivery reduces the risk of infection in the newborn. This approach has been hampered by logistical difficulties in identifying colonized women before delivery; the results of vaginal cultures early in pregnancy are poor predictors of carrier status at delivery. The Centers for Disease Control and Prevention recommends screening for anogenital colonization at 35–37 weeks of pregnancy by a swab culture of the lower vagina and anorectum; intrapartum chemoprophylaxis is recommended for culture-positive women. Intrapartum chemoprophylaxis regardless of culture status is also recommended for women who have previously given birth to an infant with group B streptococcal infection (such as this patient) or have a history of group B streptococcal bacteriuria during pregnancy.

III-88. **The answer is D.** *(Chap. 144)* Enterococci are normal inhabitants of the large bowel of human adults, although they usually make up <1% of the culturable intestinal microflora. In the healthy human gastrointestinal tract, enterococci are typical symbionts that coexist with other gastrointestinal bacteria. According to the National Healthcare Safety Network of the Centers for Disease Control and Prevention, enterococci are the second most common organisms (after staphylococci) isolated from hospital-associated infections in the United States. Although *Enterococcus faecalis* remains the predominant species recovered from nosocomial infections, the isolation of *Enterococcus faecium* has increased substantially in the past 20 years. In fact, *E. faecium* is now almost as common as *E. faecalis* as an etiologic agent of hospital-associated infections. This point is important, because *E. faecium* is by far the most resistant and challenging enterococcal species to treat; indeed, more than 80% of *E. faecium* isolates recovered in U.S. hospitals are resistant to vancomycin, and more than 90% are resistant to ampicillin (historically the most effective β-lactam agent against enterococci). Resistance to vancomycin and ampicillin in *E. faecalis* isolates is much less common (~7% and ~4%, respectively). Two meta-analyses have found that, independent of the patient's clinical status, vancomycin-resistant enterococci infection increases the risk of death over that among individuals infected with a glycopeptide-susceptible enterococcal strain.

III-89. **The answer is B.** *(Chap. 144)* Bacteremia without endocarditis is one of the most common presentations of enterococcal disease. Intravascular catheters and other devices are commonly associated with these bacteremic episodes. Other well-known sources of enterococcal bacteremia include the gastrointestinal and hepatobiliary tracts; pelvic and intra-abdominal foci; and, less frequently, wound infections, urinary tract infections (UTIs), and bone infections. In the United States, enterococci are ranked second (after coagulase-negative staphylococci) as etiologic agents of central line–associated bacteremia. Enterococci are also well-known causes of nosocomial UTI. Enterococcal UTIs are usually associated with indwelling catheterization, instrumentation, or anatomic abnormalities of the genitourinary tract, and it is often challenging to differentiate between true infection and colonization (particularly in patients with chronic indwelling catheters). The presence of leukocytes in the urine in conjunction with systemic manifestations (e.g., fever) or local signs and symptoms of infection with no other explanation and a positive urine culture (≥105 colony-forming units/mL) suggests the diagnosis. Moreover, enterococcal UTIs often occur in critically or chronically ill patients whose comorbidities may obscure the diagnosis. In many cases, removal of the indwelling catheter may suffice to eradicate the organism without specific antimicrobial therapy. Enterococcal meningitis is an uncommon disease (accounting for only ~4% of meningitis cases) that is usually associated with neurosurgical interventions and conditions such as shunts, central nervous system trauma, and cerebrospinal fluid leakage.

III-90. **The answer is B.** *(Chap. 144)* This patient has enterococcal endocarditis, which often occurs in patients with underlying gastrointestinal pathology. *Enterococcus faecalis* is a more common causative organism than *E. faecium* in community-acquired endocarditis. Patients tend to more commonly be male with underlying chronic disease. The typical presentation is one of subacute bacterial endocarditis with involvement of the mitral and/or aortic valves. Complications requiring valve replacement are not uncommon. Enterococci are intrinsically resistant and/or tolerant to several antimicrobial agents (with tolerance defined as lack of killing by drug concentrations 16 times higher than the minimal inhibitory concentration). Monotherapy for endocarditis with a β-lactam antibiotic (to which many enterococci are tolerant) has produced disappointing results, with low cure rates at the end of therapy. For many years, recommendations were to add an aminoglycoside to a cell wall–active agent (a β-lactam or a glycopeptide) to increase cure rates and eradicate the organisms; moreover, this combination is synergistic and bactericidal in vitro. However, this combination is associated with high rates of nephrotoxicity and ototoxicity. Multiple studies have now suggested synergistic combinations of ampicillin and ceftriaxone are noninferior to ampicillin with an aminoglycoside in terms of curing the infection, with far lower rates of adverse drug events.

III-91. **The answer is A.** *(Chap. 145)* Immunity to diphtheria induced by childhood vaccination gradually decreases in adulthood. An estimated 30% of men age 60–69 years old have antitoxin titers below the protective level. In addition to older age and lack of vaccination, risk factors for diphtheria outbreaks include alcoholism, low socioeconomic status, crowded living conditions, and Native American ethnic background. *Corynebacterium diphtheriae* is transmitted via the aerosol route, usually during close contact with an infected person. There are no significant reservoirs other than humans. Cutaneous diphtheria is usually a secondary infection that follows a primary skin lesion due to trauma, allergy, or autoimmunity. Most often, these isolates lack the toxin gene and thus do not express diphtheria toxin.

III-92. **The answer is D.** *(Chap. 175)* This is a classic clinical description and oral examination of diphtheria. While in many regions diphtheria has been controlled in recent years with effective vaccination, there have been sporadic outbreaks in the United States and Europe. Diphtheria is still common in the Caribbean, Latin America, and the Indian subcontinent, where mass immunization programs are not enforced. Large-scale epidemics of diphtheria have occurred in the post–Soviet Union independent states. Additional outbreaks have recently been reported in Africa and Asia. In temperate regions, respiratory diphtheria occurs year-round but is most common during winter months. The clinical diagnosis of diphtheria is based on the constellation of sore throat; adherent tonsillar, pharyngeal, or nasal pseudomembranous lesions; and low-grade fever. The systemic manifestations of diphtheria stem from the effects of diphtheria toxin and include weakness as a result of neurotoxicity and cardiac arrhythmias or congestive heart failure due to myocarditis. Most commonly, the pseudomembranous lesion is located in the tonsillopharyngeal region. The characteristic white pseudomembrane is caused by diphtheria toxin–mediated necrosis of the respiratory epithelial layer, producing a fibrinous coagulative exudate. Less commonly, the lesions are located in the larynx, nares, and trachea or bronchial passages. Large pseudomembranes are associated with severe disease and a poor prognosis. A few patients develop massive swelling of the tonsils and present with “bull-neck” diphtheria, which results from massive edema of the submandibular and paratracheal region and is further characterized by foul breath, thick speech, and stridorous breathing. The diphtheritic pseudomembrane is gray or whitish and sharply demarcated. Unlike the exudative lesion associated with streptococcal pharyngitis, the pseudomembrane in diphtheria is tightly adherent to the underlying tissues. Polyneuropathy and myocarditis are late toxic manifestations of diphtheria. During a diphtheria outbreak in the Kyrgyz Republic in 1999, myocarditis was found in 22% and neuropathy in 5% of 656 hospitalized patients. The mortality rate was 7% among patients with myocarditis as opposed to 2% among those without myocardial manifestations. The median time to death in hospitalized patients was 4.5 days. Myocarditis is typically associated with dysrhythmia of the conduction tract and dilated cardiomyopathy. Rheumatic fever is a postinfectious complication of group A streptococcal infection, not diphtheria.

III-93. **The answer is C.** *(Chap. 146) Listeria monocytogenes* usually enters the body via the gastrointestinal tract in foods. Listeriosis is most often sporadic, although outbreaks do occur. No epidemiologic or clinical evidence supports person-to-person transmission (other than vertical transmission from mother to fetus) or waterborne infection. In line with its survival and multiplication at refrigeration temperatures, *L. monocytogenes* is commonly found in processed and unprocessed foods of animal and plant origin, especially soft cheeses, delicatessen meats, hot dogs, milk, and cold salads; fresh fruits and vegetables can also transmit the organism. Because food supplies are increasingly centralized and normal hosts tolerate the organism well, outbreaks may not be immediately apparent.

The Food and Drug Administration has a zero-tolerance policy for *L. monocytogenes* in ready-to-eat foods.

III-94. The answer is A. *(Chap. 146)* This patient most likely has *Listeria* meningitis, a potentially devastating central nervous system infection particularly prominent in older, chronically ill adults. *L. monocytogenes* causes ~5–10% of all cases of community-acquired bacterial meningitis in adults in the United States. Case fatality rates are reported to be 15–26% and do not appear to have changed over time. This diagnosis should be considered in all older or chronically ill adults with "aseptic" meningitis. The presentation is more frequently subacute (with illness developing over several days) than in meningitis of other bacterial etiologies, and nuchal rigidity and overt meningeal signs are less common. Photophobia is infrequent. Focal findings and seizures are common in some but not all series. The cerebrospinal fluid profile in *Listeria* meningitis most often shows white blood cell counts in the range of 100–5000/μL (rarely higher); 75% of patients have counts below 1000/μL, usually with a neutrophil predominance more modest than that in other bacterial meningitides. Low glucose levels and positive results on Gram staining are found approximately 30–40% of the time. No clinical trials have compared antimicrobial agents for the treatment of *L. monocytogenes* infections. Data from in vitro and animal studies as well as observational clinical data indicate that ampicillin is the drug of choice, although penicillin also is highly active. Adults should receive IV ampicillin at high doses (2 g q6h).

III-95. The answer is B. *(Chap. 146)* *Listeria* bacteremia in pregnancy is a relatively rare but serious infection both for mother and fetus. Vertical transmission may occur, with 70–90% of fetuses developing infection from the mother. Preterm labor is common. Prepartum treatment of the mother increases the chances of a healthy delivery. Mortality among fetuses approaches 50% and is much lower in neonates receiving appropriate antibiotics. First-line therapy is with ampicillin, with gentamicin often added for synergy. This recommendation is the same for mother and child. In patients with true penicillin allergy, the therapy of choice is trimethoprim-sulfamethoxazole. There are case reports of successful therapy with vancomycin, imipenem, linezolid, and macrolides, but there is not enough clinical evidence and some reports of failure that maintain ampicillin as recommended first-line therapy.

III-96. The answer is E. *(Chap. 147)* This clinical scenario describes an unfortunate case of neonatal tetanus. In neonates, infection of the umbilical stump can result from inadequate umbilical cord care; in some cultures, for example, the cord is cut with grass or animal dung is applied to the stump. Circumcision or ear-piercing also can result in neonatal tetanus. It is caused by a powerful neurotoxin produced by the bacterium *Clostridium tetani* and does not result from bacteremia. Tetanus is diagnosed on clinical grounds, and case definitions are often used to facilitate clinical and epidemiologic assessments. The Centers for Disease Control and Prevention defines tetanus as "the acute onset of hypertonia or ... painful muscular contractions (usually of the muscles of the jaw and neck) and generalized muscle spasms without other apparent medical cause." Neonatal tetanus is defined by the World Health Organization as "an illness occurring in a child who has the normal ability to suck and cry in the first 2 days of life but who loses this ability between days 3 and 28 of life and becomes rigid and has spasms." Tetanus toxin prevents transmitter release and effectively blocks inhibitory interneuron discharge. The result is unregulated activity in the motor nervous system. During the initial symptoms, respiratory failure due to laryngeal and respiratory muscle spasms is the most common cause of death. Later (during the second week), autonomic dysfunction and cardiovascular complications are the most common cause of death.

III-97. The answer is D. *(Chap. 147)* Tetanus is an acute disease manifested by skeletal muscle spasm and autonomic nervous system disturbance. It is caused by a powerful neurotoxin produced by the bacterium *Clostridium tetani* and now a rare disease due to widespread vaccination. There were less than 50 cases reported recently in the United States, but a rising frequency in drug users has been seen. Older patients may be at higher risk due to waning immunity. The differential diagnosis of a patient presenting with tetanus includes strychnine poisoning and drug-related dystonic reactions. The diagnosis is clinical. Cardiovascular instability is common due to autonomic dysfunction and is manifest by rapid fluctuation in heart rate and blood pressure. Wound cultures will be positive in approximately 20% of cases. Metronidazole or penicillin should be administered to clear infection. Tetanus immune globulin is recommended over equine antiserum because of a lower risk of anaphylactic reactions. Recent evidence suggests that intrathecal administration is efficacious in inhibiting disease progression and improving outcomes. Muscle spasms may be treated with sedative drugs. With effective supportive care and often respiratory support, muscle function recovers after clearing toxin with no residual damage.

III-98. The answer is A. *(Chap. 148)* The patient has symptoms related to adult intestinal-colonization botulism. This form of botulism is difficult to confirm because it is poorly understood. No clear criteria are available to differentiate cases of adult intestinal-colonization botulism from other adult botulism cases. Often these cases are caused by *Clostridium baratii* type F, but the involvement of both *C. botulinum* type A and *C. butyricum* type E have been reported. Botulism following abdominal surgery or antibiotic use has sometimes been considered to be adult intestinal-colonization botulism. *Adult intestinal-colonization botulism*, a rare form that is poorly understood, is believed to have a pathology similar to that of infant botulism but occurs in adults; typically, patients have some anatomic or functional bowel abnormality or have recently used antibiotics that may help toxigenic clostridia compete more successfully against the normal bowel microbiota. Despite antitoxin treatment, relapse due to intermittent intraluminal production of toxin may be observed in patients with adult intestinal-colonization botulism. Weakness descends from the head, often rapidly, to involve the neck, arms, thorax, and legs; weakness and some cranial nerve deficits can be asymmetric. Deep tendon reflexes typically are normal or may progressively disappear. Paresthesias, while rare, have been reported. Ataxia, which has sometimes been reported, manifests not as cerebellar ataxia but rather as gait problems due to weakness or visual issues. The absence of cranial nerve palsies makes botulism highly unlikely, as does a lack of cranial nerve deficits at the onset of illness. Even when intubated, patients can sometimes respond to questions by moving their fingers or toes unless paralysis has affected the digits. Clinical improvement follows sprouting of new nerve terminals and may take weeks to months. Patients often require outpatient rehabilitation therapy and may experience residual deficits. Death in untreated botulism is usually due to airway obstruction from pharyngeal muscle paralysis and inadequate tidal volume resulting from paralysis of diaphragmatic and accessory respiratory muscles. Death can also result from hospital-associated infections and other sequelae of long-term paralysis, hospitalization, and mechanical ventilation.

III-99. The answer is B. *(Chap. 149)* Both of these patients have enteritis necroticans caused by *Clostridium perfringens*. In Papua New Guinea during the 1960s, enteritis necroticans (known in that locale as pigbel) was found to be the most common cause of death in childhood; it was associated with pig feasts and occurred both sporadically and in outbreaks. IM immunization against the β-toxin resulted in a decreased incidence of the disease in Papua New Guinea, although the condition remains common. *C. perfringens* is also the cause of gas gangrene myonecrosis, a highly morbid and mortal condition. The most common cause of bacterial pneumonia is the pneumococcus. *Neisseria meningitidis* and *Streptococcus pneumoniae* are the most common causes of meningitis in adults. Group A *Streptococcus* is the most common cause of bacterial pharyngitis, and staphylococcal and streptococcal species are the most common causes of cellulitis.

III-100. The answer is A. *(Chap. 149)* Clostridia are gram-positive spore-forming obligate anaerobes that reside normally in the gastrointestinal (GI) tract. Several clostridial species can cause severe disease. *Clostridium perfringens*, which is the second most common clostridial species to normally colonize the GI tract, is associated with food poisoning, gas gangrene, and myonecrosis. *C. septicum* is seen often in conjunction with GI tumors. *C. sordellii* is associated with septic abortions. All can cause a fulminant overwhelming bacteremia, but this condition is rare. The fact that this patient is well several days after his acute complaints rules out this fulminant course. A more common scenario is transient, self-limited bacteremia due to transient gut translocation during an episode of gastroenteritis. There is no need to treat when this occurs, and no further workup is necessary. *Clostridium* spp. sepsis rarely causes endocarditis because overwhelming disseminated intravascular coagulation and death occur so rapidly. Screening for GI tumor is warranted when *C. septicum* is cultured from the blood or a deep wound infection.

III-101. The answer is D. *(Chap. 150)* A high proportion of young adults and adolescents (up to 25% in some studies) are colonized with *Neisseria meningitidis*, likely due to lifestyle and high-risk activities (kissing, crowded living conditions). Changes in living conditions (e.g., freshman year of college) are associated with a higher risk of invasive infections. It is unlikely that treating noninvasive meningococcal colonization would be effective in reducing the risk of invasive disease given the likelihood of recolonization. However, the quadrivalent meningococcal vaccine is effective in preventing invasive meningococcal disease and is recommended for all children older than age 11 years.

III-102. The answer is B. *(Chap. 150)* Close contacts of individuals with known or presumed meningococcal disease are at increased risk of developing secondary disease with reports of secondary cases in up to 3% of primary cases. The rate of secondary cases is highest during the week after presentation of the index case, with most cases presenting within 6 weeks. Increased risk remains for up to 1 year. Prophylaxis is recommended for persons who are intimate with and/or household contacts of the index case and health care workers who have been directly exposed to respiratory secretions. Mass prophylaxis is not usually offered. The aim of prophylaxis is to eradicate colonization of close contacts with the strain that has caused invasive disease. Prophylaxis should be given as soon as possible to all contacts at the same time to avoid recolonization. Waiting for culture is not recommended. Ceftriaxone as a single dose is currently the most effective option in reducing carriage. Rifampin is no longer the optimal agent because it requires multiple doses and fails to eliminate carriage in up to 20% of cases. In some countries, ciprofloxacin or ofloxacin is used, but resistance has been reported in some areas. Current conjugated vaccines do not include *Neisseria meningitides* serotype B. Most sporadic cases in the United States are now due to this serotype. Vaccination should be offered in cases of meningococcal disease due to documented infection by a serotype included in the current vaccine.

III-103. The answer is A. (*Chap. 150,* https://www.cdc.gov/vaccines/vpd/mening/hcp/who-vaccinate-hcp.html) The quadrivalent conjugate vaccine currently recommended in the United States is MenACWY. This vaccine is now recommended by the Advisory Committee on Immunization Practices (ACIP) for routine administration to individuals 11–18 years of age. Since protection wanes, the Centers for Disease Control and Prevention recommends a booster dose at age 16 years. This booster dose provides protection during the ages when adolescents are at highest risk of meningococcal disease. For adolescents who receive the first dose at age 13 through 15 years, administer a booster dose at age 16 through 18 years, before the period of increased risk. Adolescents who receive their first dose of MenACWY vaccine at or after age 16 years do not need a booster dose. These vaccines are also recommended for high-risk persons from 2 months to 55 years of age. Adults should receive a MenACWY vaccine if they have complement component deficiency (e.g., C5-C9, properdin, factor H, factor D, or are taking a complement inhibitor); they have functional or anatomic asplenia (including patients with sickle cell disease); they are living with HIV; they are a microbiologist who is routinely exposed to *Neisseria meningitidis;* they are traveling or residing in countries in which the disease is common; they are part of a population at increased risk because of a serogroup A, C, W or Y meningococcal disease outbreak; they are a first-year college student living in a residence hall; or they are a military recruit. Older adults who do not have one of these risk factors do not need the MenACWY vaccine.

III-104. The answer is B. *(Chap. 151)* The patient's Gram stain shows gram-negative intracellular monococci and diplococci. In the setting of her symptoms, this is diagnostic of gonorrhea. Unfortunately, antibiotic resistance to the gonococcus has been steadily rising. The importance of adequate treatment with a regimen that the patient will adhere to cannot be

TABLE III-104 Recommended Treatment for Gonococcal Infections: Adapted from the 2015 Guidelines of the Centers for Disease Control and Prevention

Diagnosis	Treatment of Choice[a]
Uncomplicated gonococcal infection of the cervix, urethra, pharynx[b], or rectum	
First-line regimen	Ceftriaxone (250 mg IM, single dose)
	Plus
	Azithromycin (1 g PO, single dose)
Alternative regimens[c]	Cefixime (400 mg PO, single dose) ***or*** ceftizoxime (500 mg IM, single dose) ***or*** cefotaxime (500 mg IM, single dose) ***or*** spectinomycin (2 g IM, single dose)[d,e] ***or*** cefotetan (1 g IM, single dose) plus probenecid (1 g PO, single dose)[d] ***or*** cefoxitin (2 g IM, single dose) plus probenecid (1 g PO, single dose)[d]
	Plus
	Azithromycin (1 g PO, single dose)
Epididymitis	See Chap. 131 in HPIM 20
Pelvic inflammatory disease	See Chap. 131 in HPIM 20
Gonococcal conjunctivitis in an adult	Ceftriaxone (1 g IM, single dose)[f]
Ophthalmia neonatorum[g]	Ceftriaxone (25–50 mg/kg IV, single dose, not to exceed 125 mg)
Disseminated gonococcal infection[h]	
Initial therapy[i]	
Patient tolerant of β-lactam drugs	Ceftriaxone (1 g IM or IV q24h; recommended) ***or*** cefotaxime (1 g IV q8h) ***or*** ceftizoxime (1 g IV q8h)
Patients allergic to β-lactam drugs	Spectinomycin (2 g IM q12h)[d]
Continuation therapy[i]	Cefixime (400 mg PO bid)
Meningitis or endocarditis	See text for specific recommendations[j]

[a] True failure of treatment with a recommended regimen is rare and should prompt an evaluation for reinfection, infection with a drug-resistant strain, or an alternative diagnosis.

[b] Ceftriaxone and azithromycin are the only agents recommended for treatment of pharyngeal infection.

[c] See text for follow-up of persons with infection who are treated with alternative regimens.

[d] Spectinomycin, cefotetan, and cefoxitin, which are alternative agents, currently are unavailable or in short supply in the United States.

[e] Spectinomycin may be ineffective for the treatment of pharyngeal gonorrhea.

[f] Plus lavage of the infected eye with saline solution (once).

[g] Prophylactic regimens are discussed in the text.

[h] Hospitalization is indicated if the diagnosis is uncertain, if the patient has frank arthritis with an effusion, or if the patient cannot be relied on to adhere to treatment.

[i] All initial regimens should also include azithromycin (1 g PO, single dose) and should be continued for 24–48 hours after clinical improvement begins, at which time the switch may be made to an oral agent (e.g., cefixime) if antimicrobial susceptibility can be documented by culture of the causative organism. If no organism is isolated and the diagnosis is secure, then treatment with ceftriaxone should be continued for at least 1 week.

[j] Hospitalization is indicated to exclude suspected meningitis or endocarditis.

overemphasized. The 2015 treatment guidelines for gonococcal infections from the Centers for Disease Control and Prevention (CDC) are summarized in Table III-104. Rising minimal inhibitory concentrations of cefixime worldwide have led the CDC to discontinue its recommendation of this agent as first-line treatment for uncomplicated gonorrhea. The third-generation cephalosporin ceftriaxone in combination with azithromycin is recommended as treatment; dual therapy against gonorrhea could slow the development of resistance to either of these antimicrobial agents. Azithromycin, which also treats nongonococcal urethritis, is preferred to doxycycline because of its superior activity against gonorrhea and ease of use. In this case, doxycycline is also relatively contraindicated in pregnancy. Quinolone-containing regimens are no longer recommended in the United States as first-line treatment because of widespread resistance.

III-105. The answer is E. *(Chap. 141)* The importance of humoral immunity in host defenses against *Neisseria* infections is best illustrated by the predisposition of persons deficient in terminal complement components (C5 through C9) to recurrent bacteremic gonococcal infections and to recurrent meningococcal meningitis or meningococcemia. Gonococcal porin induces T-cell–proliferative responses in persons with urogenital gonococcal disease. A significant increase in porin-specific interleukin-4–producing CD4+ as well as CD8+ T lymphocytes is seen in individuals with mucosal gonococcal disease. Complement deficiencies, especially of the components involved in the assembly of the membrane attack complex (C5 through C9), predispose to *Neisseria* bacteremia, and persons with more than one episode of disseminated gonococcal infection should be screened with an assay for total hemolytic complement activity. Neutrophil quantitative or qualitative deficiencies (options A and D), Ig deficiencies (option B), and clonal defective lymphocyte populations (option C) have not been identified as specific risk factors for recurrent gonococcal infections.

III-106. The answer is E. *(Chap. 152)* Nasopharyngeal colonization by *Moraxella catarrhalis* is common in infancy, with colonization rates ranging between 33 and 100% and depending on geographic location. Several factors probably account for this geographic variation, including living conditions, daycare attendance, hygiene, household smoking, and population genetics. The prevalence of colonization decreases steadily with age. *M. catarrhalis* is also one of the three most common causes of childhood otitis media (the other two being *Streptococcus pneumoniae* and nontypable *Haemophilus influenzae*). Cultures of sinus puncture aspirates show that *M. catarrhalis* accounts for ~20% of cases of acute bacterial sinusitis in children and for a smaller proportion in adults. *M. catarrhalis* is the second most common bacterial cause of chronic obstructive pulmonary disease exacerbations (after *H. influenzae*).With the application of rigorous clinical criteria for defining the etiology of exacerbations (both culture positive and culture negative), ~10% of all exacerbations in the same study were caused by *M. catarrhalis*. *M. catarrhalis* rapidly acquired β-lactamases during the 1970s and 1980s; antimicrobial susceptibility patterns have remained relatively stable since that time, with >90% of strains now producing β-lactamase and thus resistant to amoxicillin. Most strains of *M. catarrhalis* are susceptible to amoxicillin/clavulanic acid, extended-spectrum cephalosporins, macrolides, trimethoprim-sulfamethoxazole, and fluoroquinolones.

III-107. The answer is D. *(Chap. 152)* Generally thought of as a disease of children, acute epiglottitis is also a disease of adults since the wide use of *Haemophilus influenzae* type B vaccination. Epiglottitis can cause life-threatening airway obstruction due to cellulitis of the epiglottis and supraglottic tissues, classically due to *H. influenzae* type B infection. However, other organisms are also common causes including nontypeable *H. influenzae*, *Streptococcus pneumoniae*, *H. parainfluenzae*, *Staphylococcus aureus*, and viral infection. The initial evaluation and treatment for epiglottitis in adults include airway management and IV antibiotics. The patient presented here is demonstrating signs of impending airway obstruction with stridor, inability to swallow secretions, and use of accessory muscles of inspiration. A lateral neck x-ray shows the typical thumb sign indicative of a swollen epiglottis. In addition, the patient has evidence of hypoventilation with carbon dioxide retention. Thus, in addition to antibiotics, this patient should also be intubated and mechanically ventilated electively under a controlled setting as he is at high risk for mechanical airway obstruction. Antibiotic therapy should cover the typical organisms outlined above and include coverage for oral anaerobes. In adults presenting without overt impending airway obstruction, laryngoscopy would be indicated to assess airway patency. Endotracheal intubation would be recommended for those with >50% airway obstruction. In children, endotracheal intubation is often recommended as laryngoscopy in children has provoked airway obstruction to a much greater degree than adults, and increased risk of mortality has been demonstrated in some series in children when the airway is managed expectantly.

III-108. The answer is D. *(Chap. 153)* HACEK organisms are a group of fastidious, slow-growing, gram-negative bacteria whose growth requires an atmosphere of carbon dioxide. These organisms do not grow on media routinely used for enteric bacteria (e.g., MacConkey agar). Species belonging to this group include several *Haemophilus* species, *Aggregatibacter* (formerly *Actinobacillus*) species, *Cardiobacterium* species, *Eikenella corrodens*, and *Kingella* *kingae*. HACEK bacteria normally reside in the oral cavity and have been associated with local infections in the mouth. They are also known to cause severe systemic infections—most often bacterial endocarditis, which can develop on either native or prosthetic valves. HACEK bacteremia is strongly predictive of underlying infective endocarditis (overall positive predictive value, 60%). The microbiology laboratory should be alerted when a HACEK organism is being considered. Most cultures that ultimately yield a HACEK organism become positive within the first week.

III-109. **The answer is B.** *(Chap. 153) Capnocytophaga canimorsus* is the most likely organism to have caused fulminant disease in this alcoholic patient following a dog bite. Patients with a history of alcoholism, asplenia, and glucocorticoid therapy are at risk of developing disseminated infection, sepsis, and disseminated intravascular coagulation. Because of increasing β-lactamase expression, recommended treatment is with ampicillin/sulbactam or clindamycin. One of these therapies should be administered to asplenic patients with a dog bite. Other species of *Capnocytophaga* cause oropharyngeal disease and can cause sepsis in neutropenic patients, particularly in the presence of oral ulcers. Eikenella and Haemophilus are common mouth flora in humans but not in dogs. Staphylococcus frequently causes sepsis but is less likely in this scenario.

III-110. **The answer is C.** *(Chap. 154)* The natural habitats for *Legionella pneumophila* are aquatic bodies, including lakes and streams. Natural bodies of water contain only small numbers of legionellae. However, once the organisms enter human-constructed aquatic reservoirs (such as drinking-water systems), they can grow and proliferate. Factors known to enhance colonization by and amplification of legionellae include warm temperatures (25–42°C) and the presence of scale and sediment. *L. pneumophila* can form microcolonies within biofilms; its eradication from drinking-water systems requires disinfectants that can penetrate the biofilm. Heavy rainfall and flooding can result in the entry of high numbers of legionellae into water-distribution systems, leading to an upsurge of cases. Large buildings over three stories high are commonly colonized with *Legionella*. Sporadic community-acquired Legionnaires disease has been linked to colonization of hotels, office buildings, factories, and even private homes. Drinking-water systems in hospitals and extended-care facilities have been the source for health care–associated Legionnaires disease. Transmission is via inhalation of bacteria-containing aerosol. The disease is not spread via zoonotic or insect vectors nor via person-to-person transmission. There is no effective vaccination for *L. pneumophila*.

III-111. **The answer is E.** *(Chap. 154)* Legionnaires disease is often included in the differential diagnosis of "atypical pneumonia," along with pneumonia due to *Chlamydia pneumoniae*, *C. psittaci*, *Mycoplasma pneumoniae*, *Coxiella burnetii*, and other viruses. The clinical similarities among atypical pneumonias include a nonproductive cough with a low frequency of grossly purulent sputum. The clinical manifestations of Legionnaires disease are usually more severe than those of most atypical pneumonias. The course and prognosis of *Legionella* pneumonia more closely resemble those of bacteremic pneumococcal pneumonia than those of pneumonia due to other atypical pathogens. Patients with community-acquired Legionnaires disease are significantly more likely than patients with pneumonia of other etiologies to be admitted to an intensive care unit on presentation. The presence of fever is almost universal. Temperatures in excess of 40°C (104°F) were seen in 20% of patients in one observational study. The mild cough of Legionnaires disease is only slightly productive. Sometimes the sputum is streaked with blood. Chest pain—either pleuritic or nonpleuritic—can be a prominent feature and, when coupled with hemoptysis, can lead to an incorrect diagnosis of pulmonary embolism. Shortness of breath is reported by one-third to one-half of patients. Gastrointestinal difficulties are often pronounced; abdominal pain, nausea, and vomiting affect 10–20% of patients. Diarrhea (watery rather than bloody) is reported in 25–50% of cases. Nonspecific symptoms—malaise, fatigue, anorexia, and headache—are seen early in the illness. Myalgias and arthralgias are uncommon but are prominent in a few patients. Upper respiratory symptoms, including coryza, are rare. Chest examination reveals rales early in the course and evidence of consolidation as the disease progresses. Abdominal examination may reveal generalized or local tenderness. Prospective comparative studies have shown that clinical manifestations are generally nonspecific and that Legionnaires disease is not readily distinguishable from pneumonia of other etiologies. Hyponatremia, elevated values in liver function tests, and hematuria also occurred more frequently in Legionnaires disease. Other laboratory abnormalities include creatine phosphokinase elevation, hypophosphatemia, serum creatinine elevation, and proteinuria. The most severe sequela, neurologic dysfunction, is rare but can be debilitating. The most common neurologic deficits in the long term—ataxia and speech difficulties—result from cerebellar dysfunction.

III-112. The answer is B. *(Chap. 154)* Despite antibiotic treatment, pneumonia from all causes remains a major source of mortality in the United States. Mortality from *Legionella* pneumonia varies from 0–11% in treated immunocompetent patients to approximately 30% if not treated effectively. Because *Legionella* is an intracellular pathogen, antibiotics that concentrate in the intracellular space are most likely to be effective. Newer macrolides and quinolones are antibiotics of choice and are effective as monotherapy. Doxycycline and tigecycline are active in vitro. Anecdotal reports have described successes and failures with trimethoprim-sulfamethoxazole and clindamycin. Aztreonam, most β-lactams, and cephalosporins cannot be considered effective therapy for *Legionella* pneumonia. For severe cases, rifampin may be initially added to azithromycin or a fluoroquinolone.

III-113. The answer is C. *(Chap. 154)* The "gold-standard" method for diagnosis of *Legionella* infection is isolation of the organism from respiratory secretions, although culture with the use of multiple selective media with dyes for 3–5 days—and sometimes up to 2 weeks for non-*L. pneumophila* species—is required (Table III-113). Although not used extensively, culture from transtracheal aspiration has the highest sensitivity. The sensitivity of bronchoscopy specimens is similar to that of sputum samples for culture on selective media; if sputum is not available, bronchoscopy specimens may yield the organism. Bronchoalveolar lavage fluid gives higher yields than bronchial wash specimens. *Legionella* cultures should be made more widely available since the urinary antigen test can diagnose only *L. pneumophila* serogroup 1. If antibody testing is performed, both acute- and convalescent-phase sera is necessary. A fourfold rise in titer is diagnostic; 12 weeks are often required for the detection of an antibody response. A single titer of 1:128 in a patient with pneumonia constitutes circumstantial evidence for Legionnaires disease; a single titer of 1:256 constitutes presumptive evidence. The detection of *Legionella*-soluble antigen in urine, which is often easier to collect than sputum, is a relatively low-cost test and is easy to perform. Urinary antigen can be detected shortly after clinical symptoms appear and for up to 10 months thereafter, even during antibiotic treatment. The test's specificity is 95–100%, and its sensitivity ranges from 70 to 90%. Its drawback is that it is reliable only for *L. pneumophila* serogroup 1, which causes ~80% of *Legionella* infections.

TABLE III-113 Utility of Special Laboratory Tests for the Diagnosis of Legionnaires Disease

Test	Sensitivity (%)	Specificity (%)
Culture		
Sputum[a]	80	100
Transtracheal aspirate	90	100
Direct fluorescent antibody staining of sputum	50–70	96–99
Urinary antigen testing[b]	70	100
Antibody serology[c]	40–60	96–99

[a] Use of multiple selective media with dyes.

[b] Reliable only for *L. pneumophila* serogroup 1.

[c] IgG and IgM testing of both acute- and convalescent-phase sera. A single titer of ≥1:256 is considered presumptive, while a fourfold rise in titer between the acute and convalescent phases is considered definitive. Titers peak at 3 months.

III-114. The answer is D. *(Chap. 155)* Pertussis is a highly communicable disease, with attack rates of 80–100% among unimmunized household contacts and 20% within households in well-immunized populations. The infection has a worldwide distribution, with cyclical outbreaks every 3–5 years (a pattern that has persisted despite widespread immunization). Pertussis occurs in all months; however, in North America, its activity peaks in autumn and winter. In developing countries, pertussis remains an important cause of infant morbidity and death. The reported incidence of pertussis worldwide has decreased as a result of improved vaccine coverage. However, coverage rates are still <60% in many developing nations; the World Health Organization estimates that 90% of the burden of pertussis is in developing regions. In unimmunized populations, pertussis incidence peaks during the preschool years, and well over half of children have the disease before reaching adulthood. In highly immunized populations such as those in North America, the peak incidence is among infants <1 year of age who have not completed the three-dose primary immunization series. Severe morbidity and high mortality rates, however, are restricted almost entirely to infants. In the United States between 1993 and 2004, all pertussis deaths and 86% of hospitalizations for pertussis involved infants ≤3 months of age. Although school-age children are the source of infection for most households, adults are often the source for cases in high-risk infants and may serve as the reservoir of infection between epidemic years.

III-115. The answer is C. *(Chap. 155)* Pertussis, due to the gram-negative bacteria *Bordetella pertussis,* is an upper respiratory infection characterized by a violent cough. Its prevalence has been dramatically reduced, but not eliminated, by widespread infant vaccination. It causes an extremely morbid and often mortal disease in infants <6 months old, particularly in the developing world. As the prevalence has been increasing in young adults and adolescents due to waning immunity, adolescents (11–18 years of age) and all unvaccinated adults should receive a dose of the adult-formulation diphtheria–tetanus–acellular pertussis vaccine. In addition, several countries, including the United States and the United Kingdom, recommend pertussis immunization specifically for health care workers and for women in the third trimester of pregnancy to increase passive transfer of maternal antibodies to the fetus. Some are recommending booster vaccination after 10 years. *B. pertussis* is also a growing pathogen in patients with chronic obstructive pulmonary disease. The clinical manifestations typically include a persistent, episodic cough developing a few days after a cold-like upper respiratory infection. The cough may become persistent. It often wakes the patient from sleep and results in posttussive vomiting. An audible whoop is present in less than half the cases. Diagnosis is with nasopharyngeal culture or DNA probe testing. There is no urinary antigen testing available. The goal of antibiotic therapy is to eradicate the organism from the nasopharynx. It does not alter the clinical course unless given early in the catarrhal phase. Macrolide antibiotics are the treatment of choice. Pneumonia is uncommon with *B. pertussis*. Cold agglutinins may be positive in infection with *Mycoplasma pneumoniae*, which is on the differential diagnosis of *B. pertussis*.

III-116. The answer is C. *(Chap. 156)* In healthy humans, *Escherichia coli* is the predominant species of gram-negative bacilli in the colonic flora; *Klebsiella* and *Proteus* species are less prevalent. Both *Staphylococcus* and *Clostridium* species are gram-positive organisms.

III-117. The answer is B. *(Chap. 156)* This patient is septic and has bacteremia from a urinary source. Initiation of appropriate empirical antimicrobial therapy early in the course of gram-negative bacilli (GNB) infections (particularly serious ones) leads to improved outcomes. The ever-increasing prevalence of multidrug resistance; the lag between published and current resistance rates; and variations in antimicrobial susceptibility by species, geographic location, regional antimicrobial use, and hospital site (e.g., intensive care units versus wards) necessitate familiarity with evolving local patterns of antimicrobial resistance for the selection of appropriate empirical therapy. In this case, understanding the patterns of antimicrobial resistance in the patient's place of residence is important. Factors predictive of resistance in a given isolate include recent antimicrobial use, a health care association (e.g., recent or ongoing hospitalization, dialysis, residence in a long-term care facility), or international travel (e.g., to Asia, Latin America, Africa, Eastern Europe). Data for 2008–2014 from the U.S. National Healthcare Safety Network indicates that the prevalence of the extended-spectrum β-lactamase (ESBL) phenotype among Enterobacteriaceae isolates varied by health care setting—i.e., 16% for short-term care, 38.6% for long-term care, and 10.7% for inpatient rehabilitation facilities—as did the prevalence of carbapenem resistance (2.8%, 12%, and 1.9%, respectively). ESBLs (e.g., CTX-M, SHV, TEM) are modified broad-spectrum enzymes that hydrolyze third-generation cephalosporins, aztreonam, and (in some instances) fourth-generation cephalosporins in addition to the drugs hydrolyzed by broad-spectrum β-lactamases. GNB that express ESBLs may also possess porin mutations that result in decreased uptake of cephalosporins, β-lactam/β-lactamase inhibitor combinations, and carbapenems, further reducing susceptibility to these β-lactam agents. To date, ESBLs are most prevalent in *Escherichia coli*, *Klebsiella pneumoniae*, and *K. oxytoca*, but these enzymes can occur in all Enterobacteriaceae. Carbapenems such as meropenem are the most reliably active β-lactam agents against ESBL-expressing strains. Clinical experience with alternatives is more limited, but, for organisms susceptible to piperacillin-tazobactam, this agent—dosed at 4.5 g q6h—may offer a carbapenem-sparing alternative. As she has a clear source of infection, vancomycin is unlikely to provide her benefit.

III-118. The answer is A. *(Chap. 156)* Uncomplicated cystitis, the most common acute urinary tract infection (UTI) syndrome, is characterized by dysuria, urinary frequency, and suprapubic pain. Fever and/or back pain suggests progression to pyelonephritis. *Escherichia coli* is the single most common pathogen for all UTI syndrome/host group combinations. Each year in the United States, *E. coli* causes 80–90% of an estimated 6–8 million episodes of uncomplicated cystitis in premenopausal women. Furthermore, 20% of women with an initial cystitis episode develop frequent recurrences. All of the other organisms can cause UTIs, although de novo infection with *Staphylococcus aureus* is rare and should prompt investigation into prior genitourinary instrumentation procedures or a hematogenous source.

III-119. The answer is A. *(Chap. 156)* At least five distinct pathotypes of intestinal pathogenic *Escherichia coli* exist: (1) Shiga toxin–producing *E. coli* (STEC), which includes the subsets enterohemorrhagic *E. coli* (EHEC) and the recently evolved Shiga toxin–producing enteroaggregative *E. coli* (ST-EAEC); (2) enterotoxigenic *E. coli* (ETEC); (3) enteropathogenic *E. coli* (EPEC); (4) enteroinvasive *E. coli*; and (5) enteroaggregative *E. coli* (EAEC). STEC/EHEC/ST-EAEC strains constitute an emerging group of pathogens that can cause hemorrhagic colitis and the hemolytic-uremic syndrome (HUS). Several large outbreaks resulting from the consumption of fresh produce (e.g., lettuce, spinach, sprouts) and of undercooked ground beef have received significant media attention. STEC strains are the fourth most commonly reported cause of bacterial diarrhea in the United States (after *Campylobacter*, *Salmonella*, and *Shigella*). O157:H7 is the most prominent serotype, but many other serogroups have been described. Domesticated ruminant animals, particularly cattle and young calves, serve as the major reservoir for STEC/EHEC. Ground or mechanically tenderized beef—the most common food source of STEC/EHEC strains—is often contaminated during processing. Furthermore, manure from cattle or other animals (including in the form of fertilizer) can contaminate produce (potatoes, lettuce, spinach, sprouts, fallen fruits, nuts, strawberries), and fecal runoff from these sources can contaminate water systems. It is estimated that <102 colony-forming units of STEC/EHEC/ST-EAEC can cause disease. Therefore, not only can low levels of food or environmental contamination (e.g., in water swallowed while swimming) result in disease, but person-to-person transmission (e.g., at daycare centers and in institutions) is an important route for secondary spread. After exposure to STEC/EHEC/ST-EAEC and a 3- to 4-day incubation period, colonization of the colon and perhaps the ileum results in symptoms. Colonic edema and an initial nonbloody secretory diarrhea may progress to the hallmark syndrome of grossly bloody diarrhea (identified by history or examination). Significant abdominal pain and fecal leukocytes are common (70% of cases), whereas fever is not; absence of fever can incorrectly lead to consideration of noninfectious conditions (e.g., intussusception and inflammatory or ischemic bowel disease).

III-120. The answer is D. *(Chap. 156)* The red color of most *Serratia marcescens* can produce distinctive clinical findings. *S. marcescens* strains and *S. rubidaea* can produce pink breast milk or hypopyon as well as pseudohemoptysis.

III-121. The answer is C. *(Chap. 157)* In recent years, hospital outbreaks caused by *Acinetobacter baumannii* have been reported worldwide, even in temperate climates. In the United States, the Centers for Disease Control and Prevention estimates that 12,000 *Acinetobacter* infections occur every year, 7300 of which are caused by multidrug-resistant strains, with 500 attributable deaths. Infections caused by *A. baumannii* occur frequently among patients admitted to intensive care units (ICUs). Risk factors for colonization and infection with this pathogen include nursing home residence; prolonged ICU stay; central venous catheterization; tracheostomy; mechanical ventilation; enteral feedings; and treatment with third-generation cephalosporins, fluoroquinolones, and carbapenems. Acquisition of carbapenem-resistant *A. baumannii* is most common among patients exposed to carbapenems. The onset of disease tends to be later than that caused by other gram-negative bacilli; however, clinical symptoms of hospital-acquired or ventilator-associated pneumonia due to *A. baumannii* are similar to those of nosocomial or ventilator-associated pneumonia due to other nosocomial pathogens. Thus, the most common indicators of infection include fever and increased sputum production.

III-122. The answer is B. *(Chap. 157)* Treatment of *Acinetobacter* infections is hampered by the remarkable ability of *A. baumannii* to upregulate or acquire antibiotic resistance determinants. The most prominent example is that of β-lactamases, including those capable of inactivating carbapenems, cephalosporins, and penicillins. These enzymes, which include the OXA-type β-lactamases (e.g., OXA-23), the metallo-β-lactamases (e.g., NDM), and rarely KPC-type carbapenemases, are typically resistant to currently available β-lactamase inhibitors such as clavulanate or tazobactam. Plasmids that harbor genes encoding these β-lactamases may also harbor genes encoding resistance to aminoglycosides and sulfur antibiotics. The end result is that carbapenem-resistant *A. baumannii* may become truly multidrug resistant. Selection of empirical antibiotic therapy when *A. baumannii* is suspected is challenging and must rely on knowledge of local epidemiology. Receipt of prompt, effective antibiotic therapy is the goal. Given the diversity of resistance mechanisms in *A. baumannii*, definitive therapy should be based on the results of antimicrobial susceptibility testing. Carbapenems (imipenem, meropenem, and doripenem but not ertapenem) have long been thought of as the agents of choice for serious *A. baumannii* infections. However, the clinical utility of carbapenems is now widely jeopardized by the production of carbapenemases, as described earlier. Sulbactam may be an alternative to carbapenems. Unlike other β-lactamase inhibitors (e.g., clavulanic acid and tazobactam), sulbactam has intrinsic activity against *Acinetobacter* species; this activity is mediated by the drug's binding to penicillin-binding protein 2 rather than by its ability to inhibit β-lactamases. Sulbactam is commercially available in a combined formulation with either ampicillin or cefoperazone and may also be available as a single agent in some countries.

Despite the absence of randomized clinical trials, sulbactam seems to be equivalent to carbapenems in clinical effectiveness against susceptible strains. Therapy for carbapenem-resistant *A. baumannii* is particularly problematic. The only currently available choices are polymyxins (colistin and polymyxin B) and tigecycline. Neither option is perfect. Polymyxins may be nephrotoxic and neurotoxic. Definition of the optimal dose and schedule for administration of polymyxins to patients in vulnerable groups (e.g., those requiring renal replacement therapy) remains challenging, and emergence of resistance in association with monotherapy is a concern. Conventional doses of tigecycline may not result in serum concentrations adequate to treat bloodstream infections. Resistance of *A. baumannii* to tigecycline may develop during treatment with this drug. *Acinetobacter* species, unlike *Clostridium difficile*, do not form spores.

III-123. The answer is B. *(Chap. 158)* This patient has essentially performed a urease breath test. In this simple test, the patient drinks a solution of urea labeled with the nonradioactive isotope 13C and then blows into a collection tube. If *Helicobacter pylori* urease is present, the urea is hydrolyzed, and labeled carbon dioxide is detected in breath samples. This patient's test is "positive"; therefore, he is infected with *H. pylori*. Essentially, all *H. pylori*–colonized persons have histologic gastritis, but only approximately 10–15% develop associated illnesses, including gastritis, gastric ulcers, duodenal ulcers, gastric lymphoma, and gastric adenocarcinoma. It is essentially lifelong unless eradicated by antibiotic treatment; thus, the subject's urease breath test will almost certainly remain positive without treatment. *H. pylori* infection is not correlated with a higher risk of colon cancer.

III-124. The answer is A. *(Chap. 158)* The two most important factors in successful *Helicobacter pylori* treatment are the patient's close compliance with the regimen and the use of drugs to which the patient's strain of *H. pylori* has not acquired resistance (Table III-124). Treatment failure following minor lapses in compliance is common and often leads to acquired resistance. To stress the importance of compliance, written instructions should be given to the patient, and minor side effects of the regimen should be explained. Increasing levels of primary *H. pylori* resistance to clarithromycin, levofloxacin, and—to a lesser extent—metronidazole are of growing concern. In most parts of the world (the main exception being northwestern Europe), the rate of primary clarithromycin resistance is sufficiently high that regimens containing clarithromycin plus one other antibiotic often fail; regimens with clarithromycin and two other antibiotics remain an option as the other two antibiotics are likely to eradicate *H. pylori* even if the strain is clarithromycin resistant. When a patient is known to have been exposed—even distantly—to clarithromycin or a fluoroquinolone, these antibiotics usually should be avoided. Resistance to amoxicillin or tetracycline is unusual, even if these antibiotics have been given previously, and resistance to metronidazole is only partial; thus, there is no need to avoid using these antibiotics whether or not they have been previously prescribed. Assessment of antibiotic susceptibilities before treatment would be optimal but is not usually undertaken because endoscopy and mucosal biopsy are necessary to obtain *H. pylori* for culture and because most microbiology laboratories are inexperienced in *H. pylori* culture.

TABLE III-124 Commonly Recommended Treatment Regimens for *Helicobacter pylori*

Regimen[a] (Duration)	Drug 1	Drug 2	Drug 3	Drug 4
Regimen 1: OCM (14 days)[b]	Omeprazole (20 mg bid[c])	Clarithromycin (500 mg bid)	Metronidazole (500 mg bid)	—
Regimen 2: OCA (14 days)[b]	Omeprazole (20 mg bid[c])	Clarithromycin (500 mg bid)	Amoxicillin (1 g bid)	—
Regimen 3: OBTM (14 days)[d]	Omeprazole (20 mg bid[c])	Bismuth subsalicylate (2 tabs qid)	Tetracycline HCl (500 mg qid)	Metronidazole (500 mg tid)
Regimen 4: concomitant (14 days)[e]	Omeprazole (20 mg bid[c])	Amoxicillin (1 g bid)	Clarithromycin (500 mg bid)	Tinidazole (500 mg bid[f])
Regimen 5: OAL (10 days)[g]	Omeprazole (20 mg bid[c])	Amoxicillin (1 g bid)	Levofloxacin (500 mg bid)	—

[a] The recommended first-line regimens for most of the world are shown in bold type.

[b] This regimen should be used only for populations in which the prevalence of clarithromycin-resistant strains is known to be <20%. In practice, this restriction limits the regimens' appropriate range mainly to northern Europe.

[c] Many authorities and some guidelines recommend doubling this dose of omeprazole, as trials show resultant increased efficacy with some antibiotic combinations. Omeprazole may be replaced with any proton pump inhibitor (PPI) at an equivalent dosage. Because extensive metabolizers of PPIs are prevalent among Caucasian populations, many authorities recommend esomeprazole (40 mg bid) or rabeprazole (20 mg bid), particularly for regimens 4 and 5.

[d] Data supporting this regimen come mainly from Europe and are based on the use of bismuth subcitrate (1 tablet qid) and metronidazole (400 mg tid). This is a recommended first-line regimen in most countries and is the recommended second-line regimen in northern Europe.

[e] This regimen may be used as an alternative to regimen 3.

[f] Metronidazole (500 mg bid) may be used as an alternative.

[g] This regimen is used as second-line treatment in many countries (particularly where quadruple or concomitant therapy is used as the first-line regimen) and as third-line treatment in others. It may be less effective where rates of fluoroquinolone use are high and is more likely to be ineffective if there is a personal history of fluoroquinolone use for previous treatment of other infections.

III-125. The answer is E. *(Chap. 158)* It is impossible to know whether the patient's continued dyspepsia is due to persistent *Helicobacter pylori* as a result of treatment failure or to some other cause. A quick noninvasive test to look for the presence of *H. pylori* is a urea breath test. This test can be done as an outpatient and gives a rapid, accurate response. Patients should not have received any proton pump inhibitors or antimicrobials in the meantime. Stool antigen test is another good option if urea breath testing is not available. If the urea breath test is positive >1 month after completion of first-line therapy, second-line therapy with a proton pump inhibitor, bismuth subsalicylate, tetracycline, and metronidazole may be indicated. If the urea breath test is negative, the remaining symptoms are unlikely due to persistent *H. pylori* infection. Serology is useful only for diagnosing infection initially, but it can remain positive and therefore be misleading in those who have cleared *H. pylori*. Endoscopy is a consideration to rule out ulcer or upper gastrointestinal malignancy but is generally preferred after two failed attempts to eradicate *H. pylori*. Figure III-125 outlines the algorithm for management of *H. pylori* infection.

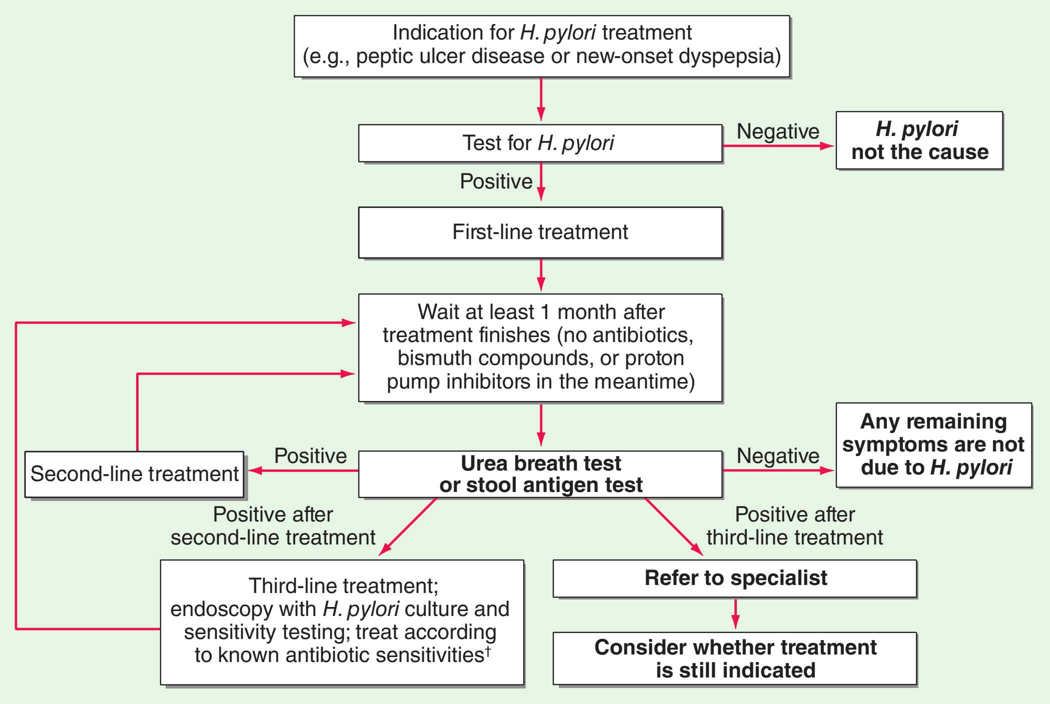

Indication for *H. pylori* treatment (e.g., peptic ulcer disease or new-onset dyspepsia)
Test for *H. pylori*
Negative
H. pylori not the cause
Positive
First-line treatment
Wait at least 1 month after treatment finishes (no antibiotics, bismuth compounds, or proton pump inhibitors in the meantime)
Second-line treatment
Positive
Urea breath test or stool antigen test
Negative
Any remaining symptoms are not due to *H. pylori*
Positive after second-line treatment
Positive after third-line treatment
Third-line treatment; endoscopy with *H. pylori* culture and sensitivity testing; treat according to known antibiotic sensitivities†
Refer to specialist
Consider whether treatment is still indicated

FIGURE III-125

III-126. The answer is D. *(Chap. 159) Stenotrophomonas maltophilia* is an opportunist that is acquired from the environment and is limited in its ability to colonize patients or cause infections. Immunocompromise alone is not sufficient to permit these events; rather, major perturbations of the human flora are usually necessary for the establishment of *S. maltophilia*. Accordingly, most cases of human infection occur in the setting of very broad-spectrum antibiotic therapy with agents such as advanced cephalosporins and carbapenems, which eradicate the normal flora and other pathogens. The remarkable ability of *S. maltophilia* to resist virtually all classes of antibiotics is attributable to the possession of antibiotic efflux pumps and of two β-lactamases (L1 and L2) that mediate β-lactam resistance, including that to carbapenems. *S. maltophilia* is most commonly found in the respiratory tract of ventilated patients, where the distinction between its roles as a colonizer and as a pathogen is often difficult to make. However, *S. maltophilia* does cause pneumonia and bacteremia in such patients, and these infections have led to septic shock. The intrinsic resistance of *S. maltophilia* to most antibiotics renders infection difficult to treat. The antibiotics to which it is most often susceptible are trimethoprim-sulfamethoxazole (TMP-SMX), ticarcillin/clavulanate, levofloxacin, and tigecycline. Of these, TMP-SMX is the agent most likely to treat *Stenotrophomonas*.

III-127. The answer is A. *(Chap. 159)* The patient likely has a ventilator-associated pneumonia caused by *Pseudomonas aeruginosa*. A potent antipseudomonal β-lactam drug (such as piperacillin-tazobactam, cefepime, or meropenem) is the mainstay of therapy (Table III-127). Failure rates were high when aminoglycosides were used as single agents, possibly because of their poor penetration into the airways and their binding to airway

TABLE III-127 Antibiotic Treatment of Infections Due to *Pseudomonas aeruginosa* and Related Species

Infection	Antibiotics and Dosages	Other Considerations
Bacteremia		
Nonneutropenic host	Ceftazidime (2 g q8h IV) *or* cefepime (2 g q8h IV) *or* piperacillin/tazobactam (3.375 g q4h IV) *or* imipenem (500 mg q6h IV) *or* meropenem (1 g q8h IV) *or* doripenem (500 mg q8h IV) ***Optional:*** Amikacin (7.5 mg/kg q12h or 15 mg/kg q24h IV)	Add an aminoglycoside for patients in shock and in regions or hospitals where rates of resistance to the primary β-lactam agents are high. Tobramycin may be used instead of amikacin (susceptibility permitting). The duration of therapy is 7 days for nonneutropenic patients. Neutropenic patients should be treated until no longer neutropenic.
Neutropenic host	Cefepime (2 g q8h IV) *or* all the other agents above (except doripenem) in the above dosages	
Endocarditis	Antibiotic regimens as for bacteremia for 6–8 weeks	Resistance during therapy is common. Surgery is required for relapse.
Pneumonia	Drugs and dosages as for bacteremia, except that the available carbapenems should not be the sole primary drugs because of high rates of resistance during therapy.	IDSA guidelines recommend the addition of an aminoglycoside or ciprofloxacin. The duration of therapy is 7 days.
Bone infection, malignant otitis externa	Cefepime or ceftazidime at the same dosages as for bacteremia; aminoglycosides are not a necessary component of therapy; ciprofloxacin (500–750 mg q12h PO) may be used	Duration of therapy varies with the drug used (e.g., 6 weeks for a β-lactam agent; at least 3 months for oral therapy except in puncture-wound osteomyelitis, for which the duration should be 2–4 weeks).
Central nervous system infection	Ceftazidime or cefepime (2 g q8h IV) *or* meropenem (1 g q8h IV)	Abscesses or other closed-space infections may require drainage. The duration of therapy is ≥2 weeks.
Eye infection		
Keratitis/ulcer	Topical therapy with tobramycin/ciprofloxacin/levofloxacin eyedrops	Use maximal strengths available or compounded by pharmacy. Therapy should be administered for 2 weeks or until the resolution of eye lesions, whichever is shorter.
Endophthalmitis	Ceftazidime or cefepime as for central nervous system infection ***plus*** Topical therapy	
UTI	Ciprofloxacin (500 mg q12h PO) *or* levofloxacin (750 mg q24h) *or* any aminoglycoside (total daily dose given once daily)	Relapse may occur if an obstruction or a foreign body is present. The duration of therapy for complicated UTI is 7–10 days (up to 2 weeks for pyelonephritis).
Multidrug-resistant *Pseudomonas aeruginosa* infection	Ceftazidime/avibactam (2.5 g q8h, infused over 2 h) *or* ceftolozane/tazobactam (1.5 g q8h) *or* colistin (100 mg q12h IV for the shortest possible period to obtain a clinical response)	Higher doses of ceftolozane/tazobactam may be required for pneumonias. The colistin doses used have varied. Dosage adjustment for colistin is required in renal failure. Inhaled colistin may be added for pneumonia (100 mg q12h).
Burkholderia cepacia infection	Meropenem (1 g q8h IV) *or* TMP-SMX (1600/320 mg q12h IV) for 14 days	Resistance to both agents is increasing. Do not use them in combination because of possible antagonism.
Melioidosis (*Burkholderia pseudomallei*), glanders (*B. mallei*)	Ceftazidime (2 g q6h) *or* meropenem (1 g q8h) *or* imipenem (500 mg q6h) for 2 weeks ***followed by*** TMP-SMX (1600/320 mg q12h PO) for 3 months	
Stenotrophomonas maltophilia infection	TMP-SMX (1600/320 mg q12h IV) ***plus*** ticarcillin/clavulanate (3.1 g q4h IV) for 14 days	Resistance to all agents is increasing. Levofloxacin or tigecycline may be alternatives, but there is little published clinical experience with these agents.

Abbreviations: IDSA, Infectious Diseases Society of America; TMP-SMX, trimethoprim-sulfamethoxazole; UTI, urinary tract infection.

secretions, so monotherapy with an aminoglycoside such as gentamicin, tobramycin, or amikacin should not be attempted. Observational studies indicate that a single modern antipseudomonal β-lactam agent to which the isolate is sensitive is as efficacious as a combination. As for the duration of therapy, Infectious Diseases Society of America/American Thoracic Society guidelines recommend 7 days of treatment for hospital-acquired pneumonia or ventilator-acquired pneumonia, even when *P. aeruginosa* is the offending organism. Recent studies suggest that extended infusions of β-lactams such as cefepime, piperacillin/tazobactam, or meropenem may result in better outcomes of *Pseudomonas* bacteremia and possibly of *Pseudomonas* pneumonia.

III-128. The answer is A. *(Chap. 159) Burkholderia cepacia* is an opportunistic pathogen that has been responsible for nosocomial outbreaks. It also colonizes and infects the lower respiratory tract of patients with cystic fibrosis, chronic granulomatous disease, and sickle cell disease. In patients with cystic fibrosis, it portends a rapid decline in pulmonary function and a poor clinical prognosis. It also may cause a resistant necrotizing pneumonia. *B. cepacia* is often intrinsically resistant to a variety of antimicrobials, including many β-lactams and aminoglycosides. Trimethoprim-sulfamethoxazole (TMP-SMX) is usually the first-line treatment. *Pseudomonas aeruginosa* and *Staphylococcus aureus* are common colonizers and pathogens in patients with cystic fibrosis. Repeated infections due to these agents will result in lung function deterioration. However, airway colonization of *B. cepacia* has the strongest risk of declining lung function and worsening function. *Stenotrophomonas maltophilia* is an opportunistic pathogen, particularly in patients with cancer, transplants, and critical illness. *S. maltophilia* is a cause of pneumonia, urinary tract infection, wound infection, and bacteremia. TMP-SMX is usually the treatment of choice for *Stenotrophomonas* infections.

III-129. The answer is B. *(Chap. 160)* All *Salmonella* infections begin with ingestion of organisms, most commonly in contaminated food or water. The infectious dose ranges from 200 to 10^6 colony-forming units, and the ingested dose is an important determinant of incubation period and disease severity. Conditions that decrease either stomach acidity (an age of <1 year, antacid ingestion, or achlorhydric disease) or intestinal integrity (inflammatory bowel disease, prior gastrointestinal surgery, or alteration of the intestinal flora by antibiotic administration) increase susceptibility to *Salmonella* infection.

III-130. The answer is E. *(Chap. 160)* Mr. Munoz is infected with a *Salmonella* species, most likely *Typhi* or *Paratyphi*. His rash is “rose spots,” the rash of enteric fever due to *S. Typhi* or *Salmonella Paratyphi*. This infection should be suspected in any individual returning from travel to a developing country, particularly from southern Asia, where the disease remains endemic, despite reporting no known potentially infected ingestion. *Salmonella* species do not ferment lactose. Further, this patient has striking relative bradycardia, a dissociation between the heart rate, and presence of fever. Most patients with such a degree of fever will be tachycardic; however, approximately 50% of patients with *Salmonella* infections will manifest this relative bradycardia. *Clostridium difficile* does not present with rash and typically not bradycardia. Travelers to South Asia are at risk of developing *Escherichia coli* infection from ingested food. However, the microbial characteristics rule out the other choices. *E. coli* and *Klebsiella pneumoniae* are both lactose fermenters. *Clostridium* is a gram-positive rod, and *Entamoeba histolytica* is a protozoan, not a bacteria.

III-131. The answer is C. *(Chap. 160)* Unlike *Salmonella Typhi* and *S. Paratyphi*, whose only reservoir is humans, *S enteritidis* can be acquired from multiple animal reservoirs and is not typically transmitted between people. Transmission is most commonly associated with food products of animal origin (especially eggs, poultry, undercooked ground meat, and dairy products), fresh produce contaminated with animal waste, and contact with animals or their environments.

S. enteritidis infection associated with chicken eggs emerged as a major cause of foodborne disease during the 1980s and 1990s. *S. enteritidis* infection of the ovaries and upper oviduct tissue of hens results in contamination of egg contents before shell deposition. Infection is spread to egg-laying hens from breeding flocks and through contact with rodents and manure. Transmission via contaminated eggs can be prevented by cooking eggs until the yolk is solidified and pasteurizing egg products. Centralization of food processing and widespread food distribution have contributed to the increased incidence of nontyphoid *Salmonella* in developed countries. Manufactured foods to which recent multistate *Salmonella* outbreaks have been traced include peanut butter; milk products, including infant formula; and various processed foods, including packaged breakfast cereal, salsa, frozen prepared meals, and snack foods. Large outbreaks also have been linked to fresh produce, including alfalfa sprouts, nuts and seeds, cantaloupe, mangoes, papayas, and tomatoes. These items become contaminated by manure or water at a single site and then are widely distributed. An estimated 6% of sporadic *Salmonella* infections in the United States are attributed to contact with reptiles or amphibians, especially iguanas, snakes, turtles, and lizards.

III-132. The answer is A. *(Chap. 161)* Because of the ready transmissibility of *Shigella*, current public health recommendations in the United States are that every case be treated with antibiotics. Ciprofloxacin is recommended as first-line treatment, but resistance to fluoroquinolones is rapidly increasing in many parts of the world. The human intestinal tract represents the major reservoir of *Shigella*, which is also found (albeit rarely) in the higher primates. Because excretion of *Shigella* is greatest in the acute phase of disease, the bacteria are transmitted most efficiently by the fecal-oral route via hand carriage; however, some outbreaks reflect foodborne or waterborne transmission. The high-level infectivity of *Shigella* is reflected by the very small inoculum required for experimental infection of volunteers (100 colony-forming units), by the very high attack rates during outbreaks in daycare centers (33–73%), and by the high rates of secondary cases among family members of sick children (26–33%). Shigellosis typically evolves through four phases: incubation, watery diarrhea, dysentery, and the postinfectious phase. The incubation period usually lasts 1–4 days but may be as long as 8 days. Typical initial manifestations are transient fever, limited watery diarrhea, malaise, and anorexia. Signs and symptoms may range from mild abdominal discomfort to severe cramps, diarrhea, fever, vomiting, and tenesmus. The manifestations are usually exacerbated in children, with temperatures up to 40–41°C (104.0–105.8°F) and more severe anorexia and watery diarrhea. This initial phase may represent the only clinical manifestation of shigellosis, especially in developed countries. Otherwise, dysentery follows within hours or days and is characterized by uninterrupted excretion of small volumes of bloody mucopurulent stools with increased tenesmus and abdominal cramps. At this stage, *Shigella* produces acute colitis involving mainly the distal colon and the rectum. Unlike most diarrheal syndromes, dysenteric syndromes rarely present with dehydration as a major feature. Toxic megacolon is a consequence of severe inflammation extending to the colonic smooth-muscle layer and causing paralysis and dilation. The postinfectious immunologic complication known as *reactive arthritis* can develop weeks or months after shigellosis, especially in patients expressing the histocompatibility antigen HLA-B27. About 3% of patients infected with *S. flexneri* later develop this syndrome, with arthritis, ocular inflammation, and urethritis—a condition that can last for months or years and can progress to difficult-to-treat chronic arthritis.

III-133. The answer is A. *(Chap. 162)* This patient is suffering from classic traveler's diarrhea of which, *Campylobacter* is a common cause. A prodrome of fever, headache, myalgia, and/or malaise often occurs 12–48 hours before the onset of diarrheal symptoms. The most common signs and symptoms of the intestinal phase are diarrhea, abdominal pain, and fever. The degree of diarrhea varies from several loose stools to grossly bloody stools; most patients presenting for medical attention have ≥10 bowel movements on the worst day of illness. Abdominal pain usually consists of cramping and may be the most prominent symptom. Pain is usually generalized but may become localized; *Campylobacter jejuni* infection may cause pseudoappendicitis. Fever may be the only initial manifestation of *C. jejuni* infection, a situation mimicking the early stages of typhoid fever. Even among patients presenting for medical attention with *Campylobacter* enteritis, not all clearly benefit from specific antimicrobial therapy. Indications for therapy include high fever, bloody diarrhea, severe diarrhea, persistence for >1 week, and worsening of symptoms. Macrolides are generally the empirical treatment of choice with <10% of isolates demonstrating resistance. A single dose of azithromycin 500 mg is effective and is the regimen of choice. A 5- to 7-day course of erythromycin (250 mg orally four times daily or—for children—30–50 mg/kg per day in divided doses) is also effective. Resistance to quinolones as well as to tetracyclines is substantial; approximately 22% of U.S. isolates in 2010 were resistant to ciprofloxacin. Except in infection with *C. fetus*, bacteremia is uncommon, developing most often in immunocompromised hosts and at the extremes of age. Due to its proclivity to cause bacteremia and distant organ involvement, *C fetus* has a far worse prognosis than other subtypes. Systemic infection with *C. fetus* is much more often fatal than that due to related species; this higher mortality rate reflects in part the population affected.

III-134. The answer is A. *(Chap. 163)* Cholera toxin consists of a monomeric enzymatic moiety (the A subunit) and a pentameric binding moiety (the B subunit). The B pentamer binds to GM1 ganglioside, a glycolipid on the surface of epithelial cells that serves as the toxin receptor and makes possible the delivery of the A subunit to its cytosolic target. The activated A subunit (A1) irreversibly transfers adenosine diphosphate (ADP)-ribose from nicotinamide adenine dinucleotide to its specific target protein, the guanosine triphosphate-binding regulatory component of adenylate cyclase. The ADP-ribosylated G protein upregulates the activity of adenylate cyclase; the result is the intracellular accumulation of high levels of cyclic adenosine monophosphate (AMP). In intestinal epithelial cells, AMP inhibits the absorptive sodium transport system in villus cells and activates the secretory chloride transport system in crypt cells, and these events lead to the accumulation of sodium chloride in the intestinal lumen. Because water moves passively to maintain osmolality, isotonic fluid accumulates in the lumen. When the volume of that fluid exceeds the capacity of the rest of the gut to resorb it, watery diarrhea results. Unless the wasted fluid and electrolytes are adequately replaced, shock (due to profound dehydration) and acidosis (due to loss of bicarbonate) follow. Fever is usually absent in cases of cholera. The stool has a characteristic appearance: a nonbilious, gray, slightly cloudy fluid with flecks of mucus, no blood, and a somewhat fishy, inoffensive odor. It has been called "rice-water" stool because of its resemblance to the water in which rice has been washed (Figure III-134).

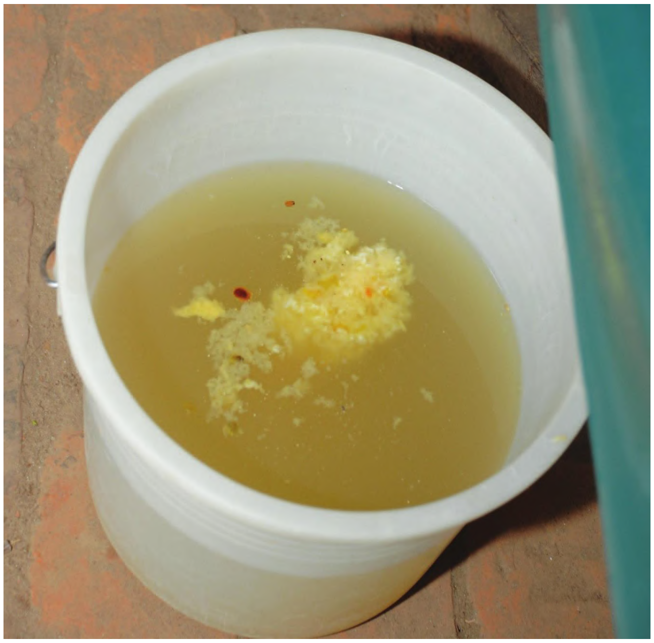


FIGURE III-134 Rice-water cholera stool. Note floating mucus and gray watery appearance. (Used with permission from Dr. ASG Faruque, International Centre for Diarrhoeal Disease Research, Dhaka.)

III-135. The answer is D. *(Chap. 163)* Cholera can be a devastating and rapidly deadly disease, but some patients, such as Mr. Zi, are only mildly affected. Table III-135 describes clinical characteristics of patients with mild, moderate, or severe dehydration due to cholera. In patients with mild dehydration, antibiotics are not needed as they are not curative. In patients with moderate or severe dehydration, the use of an antibiotic to which the organism is susceptible diminishes the duration and volume of fluid loss and hastens clearance of the organism from the stool. Erythromycin is the drug of choice. For patients with mild diarrhea from cholera, oral rehydration therapy is an excellent therapeutic option. Oral rehydration solution (ORS) takes advantage of the hexose-Na^+ cotransport mechanism to move Na^+ across the gut mucosa together with an actively transported molecule such as glucose (or galactose). Cl^- and water follow. This transport mechanism remains intact even when cholera toxin is active. ORS may be made by adding safe water to prepackaged

TABLE III-135 Assessing the Degree of Dehydration in Patients with Cholera

Degree of Dehydration	Clinical Findings
None or mild, but diarrhea	Thirst in some cases; <5% loss of total body weight
Moderate	Thirst, postural hypotension, weakness, tachycardia, decreased skin turgor, dry mouth/tongue, no tears; 5–10% loss of total body weight
Severe	Unconsciousness, lethargy, or "floppiness"; weak or absent pulse; inability to drink; sunken eyes (and, in infants, sunken fontanelles); >10% loss of total body weight

sachets containing salts and sugar or by adding a 0.5 teaspoon of table salt and 6 teaspoons of table sugar to 1 L of safe water.

III-136. The answer is E. *(Chap. 163)* All of the options can cause food-borne illnesses. However, it is important to recognize the clinical scenario of sepsis due to *Vibrio vulnificus*. While infection with *V. vulnificus* is rare, this organism is the most common cause of severe *Vibrio* infections in the United States. Like most vibrios, *V. vulnificus* proliferates in the warm summer months and requires a saline environment for growth. In the United States, infections in humans typically occur in coastal states between May and October and most commonly affect men >40 years of age. *V. vulnificus* has been linked to two distinct syndromes: primary sepsis, which usually occurs in patients with underlying liver disease (such as this patient), and primary wound infection, which generally affects people without underlying disease. Patients presenting with primary sepsis have a median incubation period of 16 hours after which they develop malaise, chills, fever, and prostration. One-third of patients develop hypotension, which is often apparent at admission. Cutaneous manifestations develop in most cases (usually within 36 hours of onset) and characteristically involve the extremities (the lower more often than the upper). In a common sequence, erythematous patches are followed by ecchymoses, vesicles, and bullae. In fact, sepsis and hemorrhagic bullous skin lesions suggest the diagnosis in appropriate settings. Necrosis and sloughing may also be evident. Laboratory studies reveal leukopenia more often than leukocytosis, thrombocytopenia, or elevated levels of fibrin-split products. *V. vulnificus* can be cultured from blood or cutaneous lesions. The mortality rate approaches 50%, with most deaths due to uncontrolled sepsis. Accordingly, prompt treatment is critical and should include empirical antibiotic administration, aggressive debridement, and general supportive care. *V. vulnificus* is sensitive in vitro to a number of antibiotics, including tetracycline, fluoroquinolones, and third-generation cephalosporins. Data from animal models suggest that either a fluoroquinolone or the combination of a tetracycline and a third-generation cephalosporin should be used in the treatment of *V. vulnificus* septicemia.

III-137. The answer is C. *(Chap. 164)* This patient has a classic presentation for chronic brucellosis. In endemic areas, brucellosis may be difficult to distinguish from the many other causes of fever. The true global prevalence of human brucellosis is unknown because of the imprecision of diagnosis and the inadequacy of reporting and surveillance systems in many countries. Recently, there has been increased recognition of the high incidence of brucellosis in India and parts of China and of importations to countries in Oceania, such as Fiji, and in Asia, such as Thailand and Vietnam. In Europe, the incidence of brucellosis in a country is inversely related to gross domestic product, and, in both developed and less well-resourced settings, human brucellosis is related to rural poverty and inadequate access to medical care. However, two features recognized in the 19th century distinguish brucellosis from other tropical fevers, such as typhoid and malaria. (1) Left untreated, the fever of brucellosis shows an undulating pattern that persists for weeks before the commencement of an afebrile period that may be followed by relapse. (2) The fever of brucellosis is associated with musculoskeletal symptoms and signs in about one-half of all patients. The clinical syndromes caused by the different species are similar, although *Brucella melitensis* tends to be associated with a more acute and aggressive presentation than *B. suis*. Vaccines based on live attenuated *Brucella* strains, such as *B. abortus* strain 19BA or 104M, have been used in some countries to protect high-risk populations but have displayed only short-term efficacy and high reactogenicity. The broad aims of antimicrobial therapy are to treat and relieve the symptoms of current infection and to prevent relapse. Tuberculosis must always be excluded, or—to prevent the emergence of resistance—therapy must be tailored to specifically exclude drugs active against tuberculosis (e.g., rifampin used alone) or to include a full anti-tuberculous regimen. Serologic examination often provides the only positive laboratory findings in brucellosis. In acute infection, IgM antibodies appear early and are followed by IgG and IgA. For adults with acute nonfocal brucellosis (duration, <1 month), a 6-week course of therapy incorporating at least two antimicrobial agents is required. Complex or focal disease may necessitate ≥3 months of therapy. The gold standard for the treatment of brucellosis in adults is IM streptomycin (0.75–1 g daily for 14–21 days) together with doxycycline (100 mg twice daily for 6 weeks). In both clinical trials and observational studies, relapse follows such treatment in 5–10% of cases. The usual alternative regimen (and the current World Health Organization recommendation) is rifampin (600–900 mg/d) plus doxycycline (100 mg twice daily) for 6 weeks. The relapse/failure rate is ~10% in trial conditions but rises to >20% in many nontrial situations, possibly because doxycycline levels are reduced and clearance rates increased by concomitant rifampin administration. Increasing evidence supports the use of an aminoglycoside such as gentamicin (5–6 mg/kg per day for at least 2 weeks) instead of streptomycin. Shorter courses have been associated with high failure rates in adults. A 5- to 7-day course of therapy with gentamicin and a 3-week course of trimethoprim-sulfamethoxazole may be adequate for children with uncomplicated disease, but prospective trials are still needed to support this recommendation. Early experience with fluoroquinolone monotherapy was disappointing, although it was suggested that ofloxacin or ciprofloxacin, given together with rifampin for 6 weeks, might be an acceptable alternative to the other 6-week regimens for adults. A substantial meta-analysis did not support the use of fluoroquinolones in first-line treatment regimens, and these drugs are not recommended by an expert consensus group (Ioannina) except in the context of well-designed clinical trials. However, a more recent meta-analysis is more supportive of the efficacy of these drugs, and an adequately powered prospective study will be needed to resolve their role in standard combination therapy. A triple-drug regimen—doxycycline and rifampin combined with an initial course of an aminoglycoside—was superior to double-drug regimens in a meta-analysis. The triple-drug regimen should be considered for all patients with complicated disease and for those for whom treatment adherence is likely to be a problem.

III-138. The answer is D. *(Chap. 165)* The patient has tularemia. Tularemia occurs widely throughout the Northern Hemisphere. The disease is nationally notifiable in the United States, and cases have been reported in all U.S. states except Hawaii. States located in the south-central and midwestern regions—specifically, Arkansas, Kansas, Missouri, and Oklahoma—account for a disproportionate number of cases. In nature, *Francisella tularensis* is maintained by arthropod and animal hosts. The bacterium is transmitted among animal hosts by arthropod bite or by direct exposure to contaminated materials in the environment. *F. tularensis* can infect and cause illness in an exceedingly broad variety of animals, having been isolated from >100 species, including domestic animals (cats and dogs). However, lagomorphs (wild hares and cottontail rabbits), terrestrial rodents (voles and meadow mice), aquatic rodents (muskrats and beavers), and ticks are thought to play a particularly significant role in propagating the organism in nature.

Most commonly, *F. tularensis* enters through the skin by tick or deerfly bite or during handling of infected wildlife (e.g., while hunting or skinning). Drugs approved by the U.S. Food and Drug Administration (FDA) for the treatment of tularemia include streptomycin, doxycycline, and tetracycline. Aminoglycosides are recommended for management of severe cases of tularemia; the primary drawback to their use is the potential for oto- and nephrotoxicity. The streptomycin dose is 1 g IM twice daily for adults and 15 mg/kg twice daily (up to a maximal daily dose of 2 g) for children; the drug is given for 10 days. Gentamicin is given IV to adults in an initial dose of 1.5–2 mg/kg followed by 1–1.7 mg/kg IV or IM every 8 hours or 5–7 mg/kg IV every 24 hours for 10–14 days, depending on the nature and severity of the infection. If aminoglycosides are contraindicated or are not readily available, tetracyclines are alternatives. Primary treatment failure and relapse occur at higher rates with tetracyclines, given their bacteriostatic mode of action; these agents are therefore recommended only for mild cases of tularemia. Tetracyclines should be administered for at least 14 days. The Infectious Diseases Society of America's guidelines for treatment of skin and soft tissue infections due to *F. tularensis* recommend treatment with oral levofloxacin (500 mg daily) or ciprofloxacin (750 mg twice daily) for at least 14 days for mild to moderate cases. Consensus-based treatment recommendations have been developed by the Working Group on Civilian Biodefense for use in the event that tularemia is used as a biological weapon. For postexposure prophylaxis, doxycycline and ciprofloxacin are the preferred choices and are administered for 14 days.

III-139. The answer is D. *(Chap. 166) Yersinia pestis* is the etiologic bacterial agent in the plague, a systemic zoonosis. Plague was introduced into North America via the port of San Francisco in 1900 as part of the Third Pandemic, which spread around the world from Hong Kong. The disease is presently enzootic on the western side of the continent from southwestern Canada to Mexico. Most human cases in the United States occur in two regions: "Four Corners" (the junction point of New Mexico, Arizona, Colorado, and Utah), especially northern New Mexico, northern Arizona, and southern Colorado, and further west in California, southern Oregon, and western Nevada. Most cases occurred from May to October—the time of year when people are outdoors and rodents and their fleas are most plentiful. Infection is most often acquired by fleabite in peridomestic environments. Infection can also be transmitted during the handling of living or dead small mammals (e.g., rabbits, hares, and prairie dogs) or wild carnivores (e.g., wildcats, coyotes, or mountain lions). Dogs and cats may bring plague-infected fleas into the home, and infected cats or dogs may transmit plague directly to humans by the respiratory route. In 2014, an outbreak of nonfatal pneumonic plague in Colorado affected four people exposed to an infected dog, with possible interhuman transmission in one case. The most recent case of person-to-person transmission in the United States before this occurred in the Los Angeles pneumonic plague outbreak of 1924.

III-140. The answer is E. *(Chap. 166)* This patient has a case of bubonic plague. Most human cases in the United States occur in two regions: "Four Corners" (the junction point of New Mexico, Arizona, Colorado, and Utah), especially northern New Mexico, northern Arizona, and southern Colorado and further west in California, southern Oregon, and western Nevada. Prairie dogs and other small mammals serve as a reservoir. After an incubation period of 2–6 days, the onset of bubonic plague is sudden and is characterized by fever (>38°C), malaise, myalgia, dizziness, and increasing pain due to progressive lymphadenitis in the regional lymph nodes near the fleabite or other inoculation site. Lymphadenitis manifests as a tense, tender swelling (bubo) that, when palpated, has a boggy consistency with an underlying hard core. Generally, there is one painful and erythematous bubo with surrounding peri-ganglionic edema. The bubo is most commonly inguinal but can also be crural, axillary, cervical, or submaxillary, depending on the site of the bite. There is often an eschar at the site of the fleabite or inoculation. *Yersinia* species are gram-negative coccobacilli (short rods with rounded ends) 1–3 μm in length and 0.5–0.8 μm in diameter. *Y. pestis* in particular appears bipolar (with a "closed safety pin" appearance) as shown in the Gram stain. The appropriate specimens for diagnosis of bubonic, pneumonic, and septicemic plague are bubo aspirate, bronchoalveolar lavage fluid or sputum, and blood, respectively. *Clostridium* and staphylococcal species are gram positive and lack the bipolar staining pattern. *Pseudomonas*, a gram-negative rod, may cause skin infections, most strikingly pyoderma gangrenosum, although this is clinically characterized by a green, foul-smelling erosion with purulent drainage as opposed to eschar and bubo formation. The filamentous fungus *Rhizopus arrhizus* is one of the most common causes of mucormycosis.

III-141. The answer is E. *(Chap. 166)* This patient has presented with terminal ileitis masquerading as appendicitis ("pseudoappendicitis"), and classic clinical manifestation of *Yersinia enterocolitica*. Older children and adults are more likely than younger children to present with abdominal pain, which can be localized to the right iliac fossa—a situation that often leads to laparotomy for presumed appendicitis (pseudoappendicitis). Appendectomy is not indicated for *Yersinia* infection causing pseudoappendicitis. Thickening of the terminal ileum and cecum is seen on endoscopy and ultrasound, with elevated round or oval lesions that may overlie Peyer patches. Mesenteric lymph nodes are enlarged. Ulcerations of the mucosa are noted on endoscopy. Consumption or preparation of raw pork products (such as chitterlings) and some processed pork products is strongly linked with infection because a high percentage of pigs carry pathogenic *Y. enterocolitica* strains. Trichinella is classically associated with consuming undercooked pork products but is associated with neuromuscular damage and inflammation as opposed to terminal ileitis. *Clostridium difficile* causes a colitis, and *Escherichia coli* can cause enteritis, although not classically associated with terminal ileitis and adenitis.

III-142. The answer is C. *(Chap. 167) Bartonella* endocarditis has been reported worldwide. Most patients are adults; more are male than female. Risk factors associated with *B. quintana* endocarditis include homelessness, alcoholism, and body louse infestation; however, individuals with no risk factors have had *Bartonella* endocarditis diagnosed as well. *B. henselae* endocarditis is associated with exposure to cats. Most cases involve native rather than prosthetic valves; the aortic valve accounts for ~60% of cases. Patients with *B. henselae* endocarditis usually have pre-existing valvulopathy, whereas *B. quintana* often infects normal valves. Clinical manifestations are usually characteristic of subacute endocarditis of any etiology. However, a substantial number of patients have a prolonged, minimally febrile or even afebrile indolent illness, with mild nonspecific symptoms lasting weeks or months before the diagnosis is made. Initial echocardiography may not show vegetations. Acute, aggressive disease is rare. Blood cultures, even with use of special techniques (lysis centrifugation or ethylenediaminetetraacetic acid-containing tubes), are positive in only ~25% of cases—mostly those caused by *B. quintana* and only rarely those caused by *B. henselae*. Prolonged incubation of cultures (up to 6 weeks) is required. Serologic tests—either immunofluorescence or enzyme immunoassay—usually demonstrate high-titer IgG antibodies to *Bartonella*. Because of cross-antigenicity, routine serology does not distinguish between *B. quintana* and *B. henselae* and may also be low-titer cross-reactive with other pathogens, such as *C. burnetii* and *Chlamydia* species. Identification of *Bartonella* to the species level is usually accomplished by application of polymerase chain reaction and DNA sequencing methods to valve tissue.

III-143. The answer is B. *(Chap. 167)* This patient has a history classic for typical cat-scratch disease (CSD) due to *Bartonella henselae*. In the immunocompetent, it is usually a self-limited illness. CSD has two general clinical presentations. Typical CSD, the more common, is characterized by subacute regional lymphadenopathy, whereas atypical CSD is the collective designation for numerous extranodal manifestations involving various organs. Of patients with CSD, 85–90% have typical disease. The primary lesion, a small (0.3- to 1-cm) painless erythematous papule or pustule, develops at the inoculation site (usually the site of a scratch or a bite) within days to 2 weeks in about one-third to two-thirds of patients. Lymphadenopathy develops 1–3 weeks or longer after cat contact. The affected lymph node(s) are enlarged and usually painful, sometimes have overlying erythema, and suppurate in 10–15% of cases. Axillary/epitrochlear nodes are most commonly involved; next in frequency are head/neck nodes and then inguinal/femoral nodes. Approximately 50% of patients have fever, malaise, and anorexia. A smaller proportion experience weight loss and night sweats mimicking the presentation of lymphoma. Fever is usually low-grade but infrequently rises to ≥39°C. Resolution is slow, requiring weeks (for fever, pain, and accompanying signs and symptoms) to months (for node shrinkage). Atypical disease includes Parinaud oculoglandular syndrome (granulomatous conjunctivitis with ipsilateral preauricular lymphadenitis), granulomatous hepatitis/splenitis, neuroretinitis (often presenting as unilateral deterioration of vision), and other ophthalmologic manifestations. In addition, neurologic involvement (encephalopathy, seizures, myelitis, radiculitis, cerebellitis, facial and other cranial or peripheral palsies), fever of unknown origin, debilitating myalgia, arthritis or arthralgia (affecting mostly women >20 years old), osteomyelitis (including multifocal disease), tendinitis, neuralgia, and dermatologic manifestations (including erythema nodosum, sometimes accompanying arthropathy) occur. For typical disease, antibiotics are not recommended. However, to rule out atypical disease, it is prudent to check laboratory studies to exclude atypical disease. For extensive lymphadenopathy (not present in this case), one may consider azithromycin 500 mg for 1 day followed by 250 mg daily for 4 days.

III-144. The answer is A. *(Chap. 167)* Bacillary angiomatosis is due to infection with *B. henselae* and occurs primarily in HIV-infected persons with CD4+ T-cell counts <100/μL but may also affect other immunosuppressed patients. Bacillary angiomatosis presents most commonly as one or more cutaneous lesions that are not painful and that may be tan, red, or purple in color. Subcutaneous masses or nodules, superficial ulcerated plaques, and verrucous growths are also seen. Nodular forms resemble those seen in fungal or mycobacterial infections. Subcutaneous nodules are often tender. In rare cases, other organs are involved in bacillary angiomatosis. Patients usually have constitutional symptoms, including fever, chills, malaise, headache, anorexia, weight loss, and night sweats. Kaposi sarcoma is also seen in immunocompromised individuals but is caused by human herpesvirus-8 infection. Bubonic plague is caused by *Yersinia pestis*, whereas pyoderma gangrenosum is most often due to *Pseudomonas* infection. Verruga peruana is due to a different *Bartonella* species, *Bartonella bacilliformis*, and is the late-onset eruptive manifestation of Carrion disease. This disease is transmitted by the phlebotomine sandfly, *Lutzomyia verrucarum*. In verruga peruana, red, hemangioma-like, cutaneous vascular lesions of various sizes appear either weeks to months after systemic illness or with no previous suggestive history. These lesions persist for months up to 1 year. Mucosal and internal lesions may also develop.

III-145. The answer is C. *(Chap. 168)* He has the classic ulcerogranulomatous penile lesion and Giemsa stain of donovanosis or granuloma inguinale, caused by *Klebsiella granulomatis*. Donovanosis has an unusual geographic distribution that includes Papua New Guinea, parts of southern Africa, India, the Caribbean, French Guyana, Brazil, and aboriginal communities in Australia. A lesion starts as a papule or subcutaneous nodule that later ulcerates after trauma. The incubation period is uncertain, but experimental infections in humans indicate a duration of approximately 50 days. Four types of lesions have been described: (1) the classic ulcerogranulomatous lesion as in this patient, a beefy red ulcer that bleeds readily when touched; (2) a hypertrophic or verrucous ulcer with a raised irregular edge; (3) a necrotic, offensive-smelling ulcer causing tissue destruction; and (4) a sclerotic or cicatricial lesion with fibrous and scar tissue. The diagnosis is confirmed by microscopic identification of Donovan bodies on Giemsa stain. Preparation of a good-quality smear is important. If donovanosis is suspected on clinical grounds, the smear for Donovan bodies should be taken before swab samples are collected to be tested for other causes of genital ulceration so that enough material can be collected from the ulcer. A swab should be rolled firmly over an ulcer previously cleaned with a dry swab to remove debris. Smears can be examined in a clinical setting by direct microscopy with a rapid Giemsa or Wright stain. Alternatively, a piece of granulation tissue crushed and spread between two slides can be used. Donovan bodies can be seen in large, mononuclear (Pund) cells as gram-negative intracytoplasmic cysts filled with deeply staining bodies that may have a safety-pin appearance (shown in the image). *Haemophilus ducreyi* is the causative organism of chancroid, which manifests in males as sexually transmitted painful genital ulcers. The recommended treatment regimens are shown in Table III-145.

TABLE III-145 Effective Antibiotics for the Treatment of Donovanosis

Antibiotic	Oral Dose
Azithromycin	1 g on day 1, then 500 mg daily for 7 days or 1 g weekly for 4 weeks
Trimethoprim-sulfamethoxazole	960 mg bid for 14 days
Doxycycline	100 mg bid for 14 days
Erythromycin	500 mg qid for 14 days (in pregnant women)
Tetracycline	500 mg qid for 14 days

III-146. The answer is E. *(Chap. 169)* The clinical presentation and microbiology are consistent with a diagnosis of nocardiosis. Nocardiosis can be caused by a number of different nocardial species. It has now been shown that nine species or species complexes are commonly associated with human disease. Most systemic disease involves *Nocardia cyriacigeorgica*, *N. farcinica*, *N. pseudobrasiliensis*, and species in the *N. transvalensis* and *N. nova* complexes. *N. brasiliensis* is usually associated with disease limited to the skin. Actinomycetoma—an indolent, slowly progressive disease of skin and underlying tissues with nodular swellings and draining sinuses—is often associated with *N. brasiliensis*, *N. otitidiscaviarum*, and *N. transvalensis* complex strains, or other actinomycetes. *N. asteroides* sensu stricto is rarely associated with human disease. However, most clinical laboratories cannot speciate isolates accurately and may identify them simply as *N. asteroides* or *Nocardia* species. The majority of cases of nocardiosis occur in patients with a host defense defect, including immunosuppression, transplantation, lymphoma, or AIDS. This patient is chronically immunosuppressed from his antirejection prophylactic regimen, which includes both glucocorticoids and tacrolimus. Pneumonia is the most common form of the disease. Patients most often have a subacute course over days to weeks, although patients who are immunosuppressed can present more acutely. Immunosuppressed patients are also more likely to produce thick sputum. Fevers, weight loss, and anorexia are common. Radiographically, single or multiple pulmonary nodules may be present and often cavitate. Nocardiosis may spread to adjacent tissues including the pericardium and mediastinum. In half of all cases of nocardiosis, disease also spreads outside the lungs with the presence of brain abscess being the most common manifestation. Other sites include skin, kidneys, bone, muscle, and eye. The characteristic Gram stain demonstrates filamentous branching gram-positive organisms. Most species of *Nocardia* are acid-fast if a weak acid is used for decolorization (e.g., modified Kinyoun method). These organisms can also be visualized by silver staining. They grow slowly in culture, and the laboratory must be alerted to the possibility of their presence on submitted specimens. Trimethoprim-sulfamethoxazole is the drug of choice for most cases. In those with intact host defenses, treatment should be continued for 6–12 months, and for those with impaired defenses, treatment should be continued for at least 12 months.

III-147. and III-148. **The answers are D and B, respectively.** *(Chap. 170)* This patient has actinomycosis. Actinomycosis occurs most frequently at an oral, cervical, or facial site, usually as a soft tissue swelling, abscess, mass, or ulcerative lesion that is often mistaken for a neoplasm. Dental diseases or procedures are common precipitating factors. The angle of the jaw is generally involved, but a diagnosis of actinomycosis should be considered with any mass lesion or relapsing infection in the head and neck. Actinomycosis is an indolent, slowly progressive infection caused by anaerobic or microaerophilic bacteria, primarily of the genus *Actinomyces*, that colonize the mouth, colon, and vagina. Mucosal disruption may lead to infection at virtually any site in the body. In vivo growth of actinomycetes usually results in the formation of characteristic clumps called *grains* or *sulfur granules*. Three "classic" clinical presentations that should prompt consideration of this unique infection are (1) the combination of chronicity, progression across tissue boundaries, and mass-like features (mimicking malignancy, with which it is often confused); (2) the development of a sinus tract, which may spontaneously resolve and recur; and (3) a refractory or relapsing infection after a short course of therapy, since cure of established actinomycosis requires prolonged treatment. Laboratory identification of the etiologic agents from the order Actinomycetales is not routine. Thus actinomycosis remains a diagnostic challenge, even for a skilled clinician. Actinomycosis requires prolonged treatment with high doses of antimicrobial agents. The need for intensive treatment is presumably due to the drugs' poor penetration of the thick-walled masses common in this infection and/or the sulfur granules themselves, which may represent a biofilm. Although therapy must be individualized, the IV administration of 18–24 million units of penicillin daily for 2–6 weeks, followed by oral therapy with penicillin or amoxicillin (total duration, 6–12 months), is a reasonable guideline for serious infections and bulky disease. For penicillin-allergic patients, tetracyclines, ceftriaxone, or carbapenems are reasonable alternatives. Combined medical-surgical therapy is still advocated in some reports. However, an increasing body of literature now supports an initial attempt at cure with medical therapy alone, even in extensive disease.

III-149. **The answer is E.** *(Chap. 171)* This patient has Whipple disease. So-called classic Whipple disease was the initial clinical syndrome recognized, with consequent identification of

Tropheryma whipplei as the causative organism. This chronic infection is defined by involvement of the duodenum and/or jejunum that develops over years. In most individuals, the initial phase of disease manifests primarily as intermittent, occasionally chronic, and rarely destructive migratory oligo- or polyarthralgias/seronegative arthritis involving the knees, wrists, and ankles most commonly. Less frequently, spondylitis, sacroiliitis, discitis, and prosthetic hip infection also have been described. Intermittent fever, myalgias, and skin nodules may accompany joint symptoms. This initial stage is often confused with a variety of rheumatologic disorders and, on average, lasts 6–8 years before gastrointestinal symptoms commence. Treatment of presumed inflammatory arthritis with immunosuppressive agents (e.g., glucocorticoids, anti–tumor necrosis factor-α) can accelerate progression of the disease process; thus screening for Whipple disease prior to initiation of immunosuppressant therapy may be appropriate, depending on the clinical scenario. Alternatively, antimicrobial therapy for another indication may reduce symptoms, and this situation should also prompt consideration of Whipple disease. The intestinal symptoms that develop in the majority of cases are characterized by diarrhea with accompanying weight loss and may be associated with fever and abdominal pain. Occult gastrointestinal blood loss, hepatosplenomegaly (10–15%), and ascites (10%) are less common. Anemia and hypereosinophilia may be detected. The most common finding on abdominal CT is mesenteric and/or retroperitoneal lymphadenopathy (usually raising concern about lymphoma). The endoscopic or video-capsule observation of pale, yellow, or shaggy mucosa with erythema or ulceration past the first portion of the duodenum suggests Whipple disease. Central nervous system (CNS) disease, defined by polymerase chain reaction-based detection of *T. whipplei* in cerebrospinal fluid (CSF), develops in ~50% of patients, many of whom are asymptomatic. A variety of neurologic manifestations have been reported and portend a poor prognosis. Endocarditis, which is increasingly recognized in Whipple disease, presents as culture-negative infection and/or congestive heart failure; hypotension occurs rarely. Embolic events or various arrhythmias or conduction defects may also be noted. Fever is often absent, and the Duke clinical criteria are rarely met. Mesenteric and retroperitoneal lymphadenopathy are common with intestinal disease, and mediastinal adenopathy may be associated with pulmonary infection. Peripheral adenopathy is less common. The diagnosis of classic Whipple disease was originally based on histologic findings in intestinal biopsy specimens, and this diagnostic procedure remains important. Infiltration of the lamina propria with macrophages containing periodic acid–Schiff-positive inclusions that are resistant to diastase is observed. Until more data become available, it seems prudent—at least in asymptomatic/symptomatic CNS disease or cardiac infection—first to administer CNS-optimized doses of IV ceftriaxone (2 g q12h) or meropenem (2 g q8h) for 2–4 weeks and then to treat with oral doxycycline or minocycline plus hydroxychloroquine or chloroquine for at least 1 year, if tolerated. Since rates of exposure to *T. whipplei*, as defined by seroprevalence, appear to be much higher than rates of chronic disease development (0.00001%), exposure rarely results in disease.

III-150. The answer is D. *(Chap. 172)* The patient presents with symptoms suggestive of lung infection; his demographics suggest that an abscess might be present, and the foul-smelling breath supports this diagnosis. His chest radiograph shows a large cavity with air-fluid level in the right lower lobe, thus confirming the diagnosis of lung abscess. Lung abscesses generally present in the dependent lobes of the lung and are often associated with aspiration of oral anaerobic bacteria that are normally found in the crevices of teeth. These organisms include *Prevotella* species, *Porphyromonas* species, non–B fragilis species of *Bacteroides*, and *Fusobacterium* species. Up to 60% of oral organisms produce β-lactamases, and penicillin alone is not recommended as initial therapy. Meropenem, β-lactam/β-lactamase inhibitor combinations, clindamycin, and metronidazole are all appropriate choices for initial coverage of the lung abscess. However, as meropenem is very broad-spectrum, narrower-spectrum agents such as ampicillin-sulbactam are preferred. Given the difficulty with isolation and identification of anaerobic organisms, empiric therapy for suspected organisms is required, and lung abscess treatment should be continued for several weeks. However, if there is no response to therapy targeted at lung abscess for several weeks, then further testing would be warranted, generally including bronchoscopy to evaluate possible malignancy. The negative interferon-γ release assay makes tuberculosis very unlikely, and the chest x-ray did not show upper lobe infiltrates or cavities.

III-151. The answer is E. *(Chap. 172)* The physician must consider several points when approaching the patient with a possible infection due to anaerobic bacteria. The organisms colonizing mucosal sites are commensals, very few of which typically cause disease. When these organisms do cause disease, it often occurs in proximity to the mucosal site they colonize. The mucosal site they have colonized is not typically infected. Meanwhile, for anaerobes to cause tissue infection, they must spread beyond the normal mucosal barriers. Conditions favoring the propagation of anaerobic bacteria, particularly a lowered oxidation-reduction potential, are necessary. These conditions exist at sites of trauma, tissue destruction, compromised vascular supply, and necrosis. Frequently, a complex array of infecting microbes can be found, occasionally with >10 different species isolated from a suppurative site. Anaerobic organisms tend to be found in abscess cavities or in necrotic tissue. Although a putrid-smelling infection site or discharge is considered diagnostic for anaerobic infection, this manifestation usually develops late in the course and is present in only 30–50% of cases. Manifestations of severe sepsis and disseminated intravascular coagulation are unusual in patients with purely anaerobic infection.

III-152. The answer is C. *(Chap. 173)* Tuberculosis is most commonly transmitted from person to person by airborne droplets. Factors that affect the likelihood of developing tuberculosis infection include the probability of contact with an infectious person, the intimacy and duration of contact, the degree of infectiousness of the contact, and the environment in which the contact takes place. The most infectious patients are those with cavitary pulmonary or laryngeal tuberculosis with about 105–107 tuberculous bacteria per milliliter of sputum. Individuals who have a negative acid-fast bacilli smear with a positive culture for tuberculosis are less infectious but may transmit the disease. However, individuals with only extrapulmonary (e.g., renal, skeletal) tuberculosis are considered to be of low infectious risk.

III-153. The answer is C. *(Chap. 173)* The World Health Organization recommends systematic testing for and treatment of latent tuberculosis infection (LTBI) for the following high-risk groups: people living with HIV, adult and child contacts of patients with infectious pulmonary TB, patients preparing for organ or hematologic transplantation, patients with silicosis, patients starting anti-tumor necrosis factor treatment, and patients on dialysis. Systematic testing for and treatment of LTBI should also be considered for prisoners, health care workers, immigrants from countries with a high TB burden, homeless persons, and illicit drug users.

III-154. The answer is A. *(Chap. 173)* The chest radiograph scan shows a right upper lobe infiltrate with a large cavitary lesion. In this man from an endemic area for tuberculosis, this finding should be treated as active pulmonary tuberculosis until proven otherwise. In addition, this patient's symptoms suggest a chronic illness with low-grade fevers, weight loss, and temporal wasting that would be consistent with active pulmonary tuberculosis. If a patient is suspected of having active pulmonary tuberculosis, the initial management should include documentation of disease while protecting health care workers and the population in general. This patient should be hospitalized in a negative-pressure room on airborne isolation until three expectorated sputum samples have been demonstrated to be negative. The samples should preferably be collected in the early morning as the burden of organisms is expected to be higher on a more concentrated sputum. The sensitivity of a single sputum for the detection of tuberculosis in confirmed cases is only 40–60%. Thus, a single sputum sample is inadequate to determine infectivity and the presence of active pulmonary tuberculosis. Skin testing with a purified protein derivative of the tuberculosis *Mycobacterium* is used to detect latent infection with tuberculosis and has no role in determining whether active disease is present. The cavitary lung lesion shown on the chest imaging could represent malignancy or a bacterial lung abscess, but given that the patient is from a high-risk area for tuberculosis, tuberculosis would be considered the most likely diagnosis until ruled out by sputum testing.

III-155. The answer is A. *(Chap. 173)* The radiograph shows bilateral small (millet seed size) nodular infiltrates consistent with disseminated or miliary tuberculosis. After primary tuberculosis infection, occult hematogenous dissemination commonly occurs. However, in the absence of a sufficient acquired immune response as in patients with advanced HIV infection, disseminated or miliary disease may result. Postprimary tuberculosis, also referred to as reactivation or secondary tuberculosis, is probably most accurately termed adult-type tuberculosis because it may result from endogenous reactivation of distant latent tuberculosis infection or recent infection (primary infection or reinfection). It is usually localized to the apical and posterior segments of the upper lobes, where the substantially higher mean oxygen tension (compared with that in the lower zones) favors mycobacterial growth. The superior segments of the lower lobes are also more frequently involved. The extent of lung parenchymal involvement varies greatly, from small infiltrates to extensive cavitary disease. Pleural effusion, which is found in up to two-thirds of cases of primary infection, results from the penetration of bacilli into the pleural space from an adjacent subpleural focus. It often resolves spontaneously in immunologically competent individuals. Tuberculosis is typically characterized as pulmonary or extrapulmonary. In order of frequency, the extrapulmonary sites most commonly involved in tuberculosis are the lymph nodes, pleura, genitourinary tract, bones and joints, meninges, peritoneum, and pericardium. However, virtually all organ systems may be affected. As a result of hematogenous dissemination in HIV-infected individuals, extrapulmonary tuberculosis is seen more commonly today than in the past in settings of high HIV prevalence.

Tuberculous lymphadenitis is the most common presentation of extrapulmonary tuberculosis in both HIV-seronegative and HIV-infected patients; lymph node disease is particularly frequent among HIV-infected patients and among children. In the United States, along with children, women (particularly non-Caucasians) seem to be especially susceptible. Lymph node tuberculosis presents as painless swelling of the lymph nodes, most commonly at posterior cervical and supraclavicular sites (a condition historically referred to as scrofula).

III-156. The answer is B. *(Chap. 173)* The treatment regimen of choice for virtually all forms of drug-susceptible tuberculosis (TB) in adults consists of a 2-month initial (intensive) phase of isoniazid, rifampin, pyrazinamide, and ethambutol followed by a 4-month continuation phase of isoniazid and rifampin (Table III-156). This regimen can cure TB in >90% of patients. Treatment should be given daily throughout the course. Systematic reviews have demonstrated that the use of an intermittent thrice-weekly regimen in the intensive phase is associated with increased risk of treatment failure, relapse, and acquisition of drug resistance. Furthermore, a thrice-weekly regimen in the continuation phase only has been associated with increased rates of failure and relapse, while a twice-weekly regimen in the continuation phase increased the risk of acquisition of drug resistance as well as rates of failure and relapse. Therefore, the World Health Organization now recommends that TB treatment in all cases be administered daily. The 2016 guidelines by the American Thoracic Society, the Centers for Disease Control and Prevention, and the Infectious Diseases Society of America, while recommending daily administration of drugs, include a provision for use of intermittent thrice-weekly supervised regimens among patients who are not infected with HIV and are at low risk of relapse (i.e., have pulmonary TB caused by drug-susceptible organisms that, at the start of treatment, is noncavitary and/or sputum smear negative). The same guidelines suggest that a 4-month regimen consisting of isoniazid, rifampin, pyrazinamide, and ethambutol may be adequate for treatment of HIV-negative adults with sputum smear–negative and culture-negative pulmonary TB (i.e., paucibacillary TB). Several observational studies and randomized controlled trials have shown that treatment of HIV-associated TB with anti-TB drugs and simultaneous use of antiretroviral treatment (ART) are associated with significant reductions in mortality risk and AIDS-related events. Evidence from randomized controlled trials shows that early initiation of ART during anti-TB treatment is associated with a 34–68% reduction in mortality rates, with especially good results in patients with CD4+ T-cell counts of <50/μL. Therefore, the main aim in the management of HIV-associated TB is to initiate anti-TB treatment and to immediately consider initiating or continuing ART. All HIV-infected TB patients, regardless of CD4+ T-cell count, are candidates for ART, which optimally is initiated as soon as possible after the diagnosis of TB and within the first 8 weeks of anti-TB

TABLE III-156 Recommended Antituberculosis Treatment Regimens

	Initial Phase		Continuation Phase	
Indication	Duration, Months	Drugs	Duration, Months	Drugs
New smear- or culture-positive cases	2	HRZE[a,b]	4	HR[a,c]
New culture-negative cases	2	HRZE[a]	4	HR[a,d]
Pregnancy	2	HRE[e]	7	HR
Relapses and treatment default[f]	Tailored according to rapid drug susceptibility testing			
Failures[f]	Tailored according to rapid drug susceptibility testing			
Resistance (or intolerance) to H	Throughout (6)	RZEQ		
Resistance (or intolerance) to R	Same as for MDR-TB; see below			
MDR-TB (resistance to at least H + R)	See Tables 173-4 and 173-5 in HPIM 20			
XDR-TB	See Table 173-4 in HPIM 20			
Intolerance to Z	2	HRE	7	HR

[a] All drugs should be given daily.

[b] Streptomycin was used in the past in place of ethambutol but is no longer considered a first-line drug.

[c] A clinical trial showed that HIV-negative patients with noncavitary pulmonary tuberculosis who have negative sputum acid-fast bacilli smears after the initial phase of treatment can be given once-weekly rifapentine/isoniazid in the continuation phase. However, this regimen is rarely used.

[d] The American Thoracic Society, the Centers for Disease Control and Prevention, and the Infectious Diseases Society of America suggest that a 2-month continuation phase could be used in HIV-seronegative patients with sputum smear–negative and culture-negative TB.

[e] The 6-month regimen with pyrazinamide can probably be used safely during pregnancy and is recommended by the WHO and the International Union Against Tuberculosis and Lung Disease. If pyrazinamide is not included in the initial treatment regimen, the minimal duration of therapy is 9 months.

[f] The availability of rapid molecular methods to identify drug resistance allows initiation of a proper regimen at the start of treatment.

Abbreviations: E, ethambutol; H, isoniazid; MDR-TB, multidrug-resistant tuberculosis; Q, a quinolone antibiotic; R, rifampin; WHO, World Health Organization; XDR-TB, extensively drug-resistant tuberculosis; Z, pyrazinamide.

therapy; ART should be started within the first 2 weeks of TB treatment for profoundly immunosuppressed patients with CD4+ T-cell counts of <50/μL.

III-157. The answer is B. *(Chap. 173)* The aim of treatment of latent tuberculosis is to prevent development of active disease, and the tuberculin skin test (PPD) is the most common means of identifying cases of latent tuberculosis in high-risk groups. To perform a tuberculin skin test, 5 tuberculin units of PPD are placed subcutaneously in the forearm. The degree of induration is determined after 48–72 hours. Erythema only does not count as a positive reaction to the PPD. The size of the reaction to the tuberculin skin test determines whether individuals should receive treatment for latent tuberculosis (Table III-157). In general, individuals in low-risk groups should not be tested. However, if tested, a reaction >15 mm is required to be considered as positive. School teachers are considered low-risk individuals. Thus, the reaction of 7 mm is not a positive result, and treatment is not required. A size of ≥10 mm is considered positive in individuals who have been infected within 2 years or those with high-risk medical conditions. The individual working in an area where tuberculosis is endemic and who has tested newly positive by skin testing should be treated as a newly infected individual. High-risk medical conditions for which treatment of latent tuberculosis is recommended include diabetes mellitus, injection drug use, end-stage renal disease, rapid weight loss, and hematologic disorders. PPD reactions ≥5 mm are considered positive for latent tuberculosis in individuals with fibrotic lesions on chest radiograph, those with close contact with an infected person, and those with HIV or who are otherwise immunosuppressed. There are two situations in which treatment for latent tuberculosis is recommended regardless of the results on skin testing. First, infants and children who have had close contact with an actively infected person should be treated. After 2 months of therapy, a skin test should be performed. Treatment can be discontinued if the skin test remains negative at that time. Also, individuals who are HIV

TABLE III-157 Tuberculin Reaction Size and Treatment of Latent *Mycobacterium tuberculosis* Infection

Risk Group	Tuberculin Reaction Size (mm)
HIV-infected persons	≥5
Recent contacts of a patient with tuberculosis (TB)	≥5[a]
Organ transplant recipients	≥5
Persons with fibrotic lesions consistent with old TB on chest radiography	≥5
Persons who are immunosuppressed, e.g., due to the use of glucocorticoids or tumor necrosis factor-α inhibitors	≥5
Persons with high-risk medical conditions[b]	≥5
Recent immigrants (≤5 years) from high-prevalence countries	≥10
Injection drug users	≥10
Mycobacteriology laboratory personnel; residents and employees of high-risk congregate settings[c]	≥10
Children <5 years of age; children and adolescents exposed to adults in high-risk categories	≥10
Low-risk persons[d]	≥15

[a] Tuberculin-negative contacts, especially children, should receive prophylaxis for 2–3 months after contact ends and should then undergo repeat tuberculin skin testing (TST). Those whose results remain negative should discontinue prophylaxis. HIV-infected contacts should receive a full course of treatment regardless of TST results.
[b] These conditions include silicosis and end-stage renal disease managed by hemodialysis.
[c] These settings include correctional facilities, nursing homes, homeless shelters, and hospitals and other healthcare facilities.
[d] Except for employment purposes where longitudinal TST screening is anticipated, TST is not indicated for these low-risk persons. A decision to treat should be based on individual risk/benefit considerations.
Source: Adapted with permission from Centers for Disease Control and Prevention: TB elimination—treatment options for latent tuberculosis infection (2011).

positive and have had close contact with an infected person should be treated regardless of skin test results.

III-158. The answer is B. *(Chap. 173)* Two in vitro assays that measure T-cell release of interferon (IFN)-γ in response to stimulation with highly tuberculosis (TB)-specific antigens were introduced in the early 2000s. IFN-γ release assays (IGRAs) have previously been reported to be more specific than the tuberculosis skin test (TST) as a result of less cross-reactivity with bacillus Calmette-Guérin vaccination and sensitization by nontuberculous mycobacteria. Recent studies suggest that IGRAs may not perform well in serial testing (e.g., among health care workers) and that interpretation of results depends on cutoff values used to define positivity. Potential advantages of IGRAs include logistical convenience, the need for fewer patient visits to complete testing, and the avoidance of somewhat subjective measurements (e.g., skin induration). However, IGRAs require that blood be drawn and then delivered to the laboratory in a timely fashion. IGRAs also require that testing be performed by specially trained technicians in a laboratory setting. These requirements pose challenges similar to those faced with the TST, including cold-chain requirements and batch-to-batch variations. Because of higher specificity and greater availability of resources, IGRAs have usually replaced the TST for latent TB infection (LTBI) diagnosis in low-incidence, high-income settings. However, in high-incidence TB and HIV settings and population groups, evidence about the performance and usefulness of IGRAs is still limited, and cost considerations may currently limit wider use. However, for individuals at high risk of progression to active TB (e.g., HIV-infected persons), either test—or, to optimize sensitivity, both tests—may be used. In conclusion, both the TST and IGRAs, although useful as diagnostic aids, are imperfect tests for LTBI: while they can identify latently infected persons, they have low predictive value in identifying individuals with the highest risk of progression toward disease, cannot differentiate between active TB and LTBI, cannot distinguish new infections from reinfections, and display reduced sensitivity in immunocompromised patients.

III-159. The answer is E. *(Chap. 173)* Bacillus Calmette-Guérin (BCG) is derived from an attenuated strain of *Mycobacterium bovis*. It has been available since 1921. Many vaccines are available, but they vary in efficacy from 0–80% in clinical trials. The vaccine protects infants and young children from serious forms of tuberculosis including meningitis and miliary disease. Side effects from the vaccine are rare, but BCG dissemination (BCGitis) may occur in patients with severe combined immunodeficiency or advanced HIV-induced immunosuppression. BCG will cross-react with tuberculin skin testing, but the size of the response wanes with time. BCG vaccination is currently recommended in countries with a high TB prevalence. It is not recommended in the United States because of the low prevalence of disease and cross-reactivity with tuberculin skin testing. Infants with unknown HIV infection status, infants of mothers with known HIV infection, and HIV-infected individuals should not receive BCG.

III-160. The answer is A. *(Chap. 174)* This patient has leprosy, caused by *Mycobacterium leprae*. The spectrum from polar tuberculoid to borderline tuberculoid to mid-borderline (which is rarely encountered) to borderline lepromatous to polar lepromatous disease is associated with an evolution from asymmetric localized macules and plaques to nodular and indurated symmetric generalized skin manifestations, an increasing bacterial load, and loss of *M. leprae*–specific cellular immunity (Table III-160). This particular patient has tuberculoid leprosy as represented by a well-defined, hypopigmented, anesthetic macule with anhidrosis and a raised granular margin. Leprosy most commonly presents with both characteristic skin lesions and skin histopathology; thus, the disease should be suspected when a patient from an endemic area has suggestive skin lesions or peripheral neuropathy. The diagnosis should be confirmed by histopathology. In tuberculoid leprosy, lesional areas—preferably the advancing edge—must be biopsied because normal-appearing skin does not have pathologic features. Tuberculoid leprosy results in symptoms confined to the skin and peripheral nerves. The incubation period prior to manifestation of clinical disease can vary between 2 and 40 years, although it is generally 5–7 years in duration. This long incubation period is probably, at least in part, a consequence of the extremely long doubling time for *M. leprae* (14 days in mice versus in vitro doubling times of 1 day and 20 minutes for *M. tuberculosis* and *Escherichia coli*, respectively). Leprosy presents as

TABLE III-160 Clinical, Bacteriologic, Pathologic, and Immunologic Spectrum of Leprosy

Feature	Tuberculoid (TT, BT) Leprosy	Borderline (BB, BL) Leprosy	Lepromatous (LL) Leprosy
Skin lesions	One or a few sharply defined annular asymmetric macules or plaques with a tendency toward central clearing, elevated borders	Intermediate between BT- and LL-type lesions; ill-defined plaques with an occasional sharp margin; few or many in number	Symmetric, poorly marginated, multiple infiltrated nodules and plaques or diffuse infiltration; xanthoma-like or dermatofibroma papules; leonine facies and eyebrow alopecia
Nerve lesions	Skin lesions anesthetic early; nerve near lesions sometimes enlarged; nerve abscesses most common in BT	Hypesthetic or anesthetic skin lesions; nerve trunk palsies, at times symmetric	Hypesthesia a late sign; nerve palsies variable; acral, distal, symmetric anesthesia common
Acid-fast bacilli (BI[a])	0–1+	3–5+	4–6+
Lymphocytes	2+	1+	0–1+
Macrophage differentiation	Epithelioid	Epithelioid in BB; usually undifferentiated but may have foamy changes in BL	Foamy changes the rule; may be undifferentiated in early lesions
Langerhans giant cells	1–3+	—	—
Lepromin skin test	+++	—	—
Lymphocyte transformation test	Generally positive	1–10%	1–2%
CD4+/CD8+ T cell ratio in lesions	1.2	BB: NT; BL: 0.48	0.50
Mycobacterium leprae PGL-1 antibodies	60%	85%	95%

[a] See text.

Abbreviations: BB, mid-borderline; BI, bacteriologic index; BL, borderline lepromatous; BT, borderline tuberculoid; LL, polar lepromatous; NT, not tested; PGL-1, phenolic glycolipid l; TT, polar tuberculoid.

a spectrum of clinical manifestations that have bacteriologic, pathologic, and immunologic counterparts. Distinguishing dermatopathologic characteristics include the number of lymphocytes, giant cells, and acid-fast bacilli (AFB) as well as the nature of epithelioid cell differentiation. Where a patient presents on the clinical spectrum largely determines prognosis, complications, reactional states, and the intensity of antimicrobial therapy required. The skin lesions of tuberculoid leprosy consist of one or a few hypopigmented macules or plaques (Figure III-160) that are sharply demarcated and hypesthetic, often have erythematous or raised borders, and are devoid of the normal skin organs (sweat glands and hair follicles) and thus are dry, scaly, and anhidrotic. AFB are generally absent or few in number. Tuberculoid leprosy patients may have asymmetric enlargement of one or a few peripheral nerves. Indeed, leprosy and certain rare hereditary neuropathies are the only human diseases associated with peripheral-nerve enlargement. Although any peripheral nerve may be enlarged (including small digital and supraclavicular nerves), those most commonly affected are the ulnar, posterior auricular, peroneal, and posterior tibial nerves, with associated hypesthesia and myopathy. For treatment purposes, the World Health Organization (WHO) originally classified patients with few bacteria in the dermis (bacteriologic index [BI] <2) as paucibacillary and those with many bacteria (BI >2) as multibacillary. The WHO recommended that paucibacillary leprosy in adults be treated with 100 mg of dapsone daily and 600 mg of rifampin monthly (supervised) for 6 months. However, several factors have caused many authorities to question the WHO recommendations and to favor a more intensive approach. Among these factors are—for multibacillary patients—a high (double-digit) relapse rate in several locales (reaching 20–40% in one locale, with the rate directly related to the initial bacterial burden) and—for paucibacillary patients—demonstrable lesional activity for years in half of patients after the completion of therapy. The more intensive approach calls for tuberculoid leprosy to be treated with dapsone (100 mg/d) for 5 years.

III-161. The answer is B. *(Chap. 175)* The chest CT shows a “tree-in-bud” pattern in the peripheral right lung and bilateral bronchiectasis. The tree-in-bud pattern is consistent with bronchoalveolar inflammation and is typical of nontuberculous mycobacteria (NTM) infection. With the remarkable decline in U.S. cases of tuberculosis over recent decades, NTM have become the mycobacteria most commonly isolated from humans in North America. However, not all isolations of NTM, especially from the lung, reflect pathology and require treatment. Whereas identification of an organism in a blood or organ biopsy specimen in a compatible clinical setting is diagnostic, the American Thoracic Society (ATS) recommends that pulmonary infection due to NTM be diagnosed only when parenchymal disease is clearly demonstrable—i.e., in an appropriate clinical and radiographic setting (nodules, bronchiectasis, cavities) and with repeated isolation of NTM from expectorated sputum or recovery of NTM from bronchoscopy or biopsy specimens. Given the large number of species of NTM and the importance of accurate diagnosis for the implementation of proper therapy, identification of these organisms is ideally taken to the species level. Nontuberculous mycobacteria, such as *Mycobacterium avium* complex (MAC), may cause chronic pulmonary infections in normal hosts and those with underlying pulmonary disease immunosuppression. In normal hosts, bronchiectasis is the most common underlying condition. In immunocompetent patients without underlying disease, treatment of pulmonary infection with MAC is considered on an individual basis based on symptoms, radiographic findings, and bacteriology. The ATS has developed guidelines for the diagnosis of infection with MAC, *M. abscessus*, and *M. kansasii*. A positive diagnosis requires the growth of NTM from two of three sputum samples, regardless of smear findings; a positive bronchoscopic alveolar sample, regardless of smear findings; or a pulmonary parenchyma biopsy sample with granulomatous inflammation or mycobacteria found on section and NTM found on culture. NTM cause chronic infections that evolve relatively slowly over a period of weeks to years. Therefore, it is rarely necessary to initiate treatment on an emergent basis before the diagnosis is clear and the infecting species is known. Treatment of NTM is complex, often poorly tolerated, and potentially toxic. Just as in tuberculosis, inadequate single-drug therapy is almost always associated with the emergence of antimicrobial resistance and relapse. This is especially true if a patient is empirically treated for a pneumonia with single-drug therapy with a macrolide (such as azithromycin or clarithromycin) or a fluoroquinolone (such as moxifloxacin or levofloxacin). MAC infection often requires multidrug therapy, the foundation of which is a macrolide (clarithromycin or azithromycin), ethambutol, and a rifamycin (rifampin or rifabutin). For pulmonary MAC disease, thrice-weekly administration of a macrolide, a rifamycin, and ethambutol has been successful. Therapy is prolonged, generally continuing for 12 months after culture conversion; typically, a course lasts for at least 18 months. Other drugs with activity against MAC organisms include IV and aerosolized aminoglycosides, fluoroquinolones, and clofazimine. In elderly patients, rifabutin can exert significant toxicity. However, with only modest efforts, most antimycobacterial regimens are well tolerated by most patients. Resection of cavitary lesions or severely bronchiectatic segments has been advocated for some patients, especially those with macrolide-resistant infections. The success of therapy for pulmonary MAC infections depends on whether disease is nodular or cavitary and on whether it is early or advanced, ranging from 20 to 80%.

III-162. The answer is A. *(Chap. 175)* Nontuberculous mycobacteria (NTM) can be classified as “fast-growers” and “slow-growers” based on the length of time they took to grow in culture. Although more sophisticated tests have been developed, this classification scheme is still used and is of some benefit to the clinician. Fast-growing NTMs include *Mycobacterium abscessus*, *M. fortuitum*, and *M. chelonae*. They will typically take 7 days or less to grow on standard media, allowing relatively fast identification and drug-resistance testing. Slow-growing NTM include *M. avium*, *M. marinum*, *M. ulcerans*, and *M. kansasii*. They often require special growth media and therefore a high pretest suspicion. The patient described in this case likely has a cutaneous infection from one of the “fast-growing” NTMs, which could be diagnosed with tissue biopsy, Gram stain, and culture.

III-163. The answer is C. *(Chap. 176)* Pyrazinamide (PZA) is first-line treatment for *Mycobacterium tuberculosis*. The addition of PZA for 2 months to isoniazid and rifampin allows the total duration of treatment to be shortened from 9 months to 6 months. PZA has no utility in the treatment of nontuberculous mycobacteria. Ethambutol has no serious drug interactions, but patients must be closely monitored for optic neuritis, which may manifest with decreased visual acuity, central scotoma, or difficulty seeing green (or red). All patients initiating therapy with ethambutol should have a visual and ophthalmologic examination at baseline. In the United States overall, isoniazid resistance remains uncommon. Primary isoniazid resistance is more common in patients with tuberculosis born outside the United States. Rifampin is a potent inducer of the cytochrome P450 system and has numerous drug interactions. The Centers for Disease Control and Prevention has guidelines for managing antituberculosis drug interactions including rifampin (www.cdc.gov/tb/). Rifabutin is a less potent inducer of hepatic cytochromes. Rifabutin is recommended for HIV-infected patients who are on antiretroviral therapy with protease inhibitors or nonnucleoside reverse transcriptase inhibitors (particularly nevirapine) in place of rifampin.

III-164. The answer is B. *(Chap. 177)* The patient’s history of unprotected intercourse, a recent painless penile ulcer suspicious for a primary chancre, and the subsequent maculopapular rash involving the palms/soles is consistent with secondary syphilis. The lesion of primary syphilis is typically a painless, indurated papule that is typically located at the site of inoculation. In heterosexual men, it is typically located on the penis, although it can be variably found on the anus, rectum, lips, or oropharynx. The primary chancre typically heals spontaneously within 3–6 weeks, and because it is painless, some patients with primary syphilis do not initially seek medical attention. Secondary syphilis is sometimes described as the “great imitator” because its manifestations are protean. Common manifestations include mucocutaneous lesions and nontender lymphadenopathy but less commonly include meningitis, hepatitis, nephropathy, gastrointestinal involvement, arthritis, periostitis, or ocular findings. The preferred therapy for patients for primary, secondary, or early latent syphilis without neurologic or ocular involvement and without confirmed penicillin allergy is a single dose of IM benzathine penicillin G. For patients with late latent syphilis (or latent syphilis of unknown duration), three doses of benzathine penicillin G over 3 weeks is preferred. Two weeks of IV penicillin G is recommended for treatment of neurosyphilis or ocular syphilis. Evaluation of the cerebrospinal fluid is not mandatory in the absence of signs or symptoms or nervous system involvement, a rapid plasma reagin ≥1:32, HIV infection, CD4 ≤350/μL, or suspected treatment failure. Tetracycline and doxycycline can be considered in patients with confirmed penicillin allergy or in the case of drug shortages but are not preferred in patients without penicillin allergy. Due to the increasing prevalence of macrolide resistance, azithromycin is not recommended.

III-165. The answer is B. *(Chap. 177)* Syphilitic involvement of the central nervous system can occur in both early or late syphilis and ranges from asymptomatic neurosyphilis, meningeal syphilis, meningovascular syphilis, and general paresis to tabes dorsalis. Although meningeal syphilis usually occurs within the first year after infection, general paresis usually presents at least 10 years after infection, and tabes dorsalis usually presents after decades of latent infection. This patient has symptoms of tabes dorsalis. Tabes dorsalis is a late manifestation of syphilis that presents as symptoms and signs of demyelination of the posterior columns, dorsal roots, and dorsal root ganglia, including ataxia, foot drop, paresthesia, bladder disturbances, impotence, areflexia, and loss of positional, deep-pain, and temperature sensations. The small, irregular Argyll Robertson pupil, a feature of both tabes dorsalis and paresis, reacts to accommodation but not to light. Both pupils are typically involved. The pupils are typically small and do not dilate fully in dim light. However, the pupils constrict to near vision and dilate to far vision. Optic atrophy also occurs frequently in association with tabes.

III-166. The answer is D. *(Chap. 177)* Serologic testing for syphilis includes nontreponemal and treponemal tests. Of nontreponemal tests, the rapid plasma reagin (RPR) test is easier to perform and uses unheated serum or plasma; it is the test of choice for rapid serologic diagnosis in a clinical setting. The VDRL test remains the standard for examining cerebrospinal fluid and is superior to the RPR for this purpose. The RPR and VDRL tests are recommended for screening and for quantitation of serum antibody. The titer reflects disease activity, rising during the evolution of early syphilis, often exceeding 1:32 in secondary syphilis, and declining slowly thereafter without therapy. False-positive results increase with increasing age, approaching 10% in patients >70 years old.

Treponemal tests measure antibodies to native or recombinant *Treponema pallidum* antigens and include the fluorescent treponemal antibody–absorbed (FTA-ABS) test and the *T. pallidum* particle agglutination (TPPA) test, both of which are more sensitive for primary syphilis than the lipoidal tests. When used to confirm reactive nontreponemal test results, treponemal tests have a very high positive predictive value for diagnosis of syphilis. Treponemal enzyme or chemiluminescence immunoassays (EIAs/CIAs), based largely on reactivity to recombinant antigens, are now widely used as screening tests by large laboratories. When used for screening, however, standard treponemal tests give false-positive results at rates as high as 1–2%, but the rate is much higher with the EIA/CIA tests. A high proportion of sera that are reactive by EIA/CIA are nonreactive by nontreponemal tests. Such sera should be examined in the TPPA test, which includes different antigens and a different platform. If the TPPA test is nonreactive, the patient is unlikely to have syphilis; if it is reactive, the patient is likely to have current or past syphilis.

III-167. The answer is B. *(Chap. 177)* All *Treponema pallidum*–infected patients who have signs or symptoms consistent with neurologic disease (e.g., meningitis, hearing loss) or ophthalmic disease (e.g., uveitis, iritis) should have a cerebrospinal fluid (CSF) examination, regardless of disease stage. Specifically, patients with rapid plasmin reagin (RPR) titers of ≥1:32 are at higher risk of having neurosyphilis (11- and 6-fold higher in HIV-infected and HIV-uninfected persons, respectively), as are HIV-infected patients with CD4+ T-cell counts of ≤350/μL. Persons with active tertiary syphilis and those in whom treatment failure is suspected also should have their CSF examined. Involvement of the central nervous system is detected by examination of CSF for mononuclear pleocytosis (>5 white blood cells/μL), increased protein concentration (>45 mg/dL), or CSF VDRL reactivity. Elevated CSF cell counts and protein concentrations are not specific for neurosyphilis and may be confounded by HIV co-infection. Because CSF pleocytosis may also be due to HIV, some studies have suggested using a CSF white-cell cutoff of 20 cells/μL as diagnostic of neurosyphilis in HIV-infected patients with syphilis. The CSF VDRL test is highly specific and, when reactive, is considered diagnostic of neurosyphilis; however, this test is insensitive and may be nonreactive even in cases of symptomatic neurosyphilis. The RPR test should not be substituted by the VDRL test for CSF examination. In addition, he should have his serum tested for syphilis, partially as the RPR can be followed clinically as a sign of appropriate response to treatment. The RPR test is easier to perform and uses unheated serum or plasma; it is the test of choice for rapid serologic diagnosis in a clinical setting. Clinicians need to be familiar with three uses of serologic tests for syphilis recommended by the Centers for Disease Control and Prevention: (1) screening or diagnosis (RPR or VDRL), (2) quantitative measurement of antibody to assess clinical syphilis activity or to monitor response to therapy (RPR or VDRL), and (3) confirmation of a syphilis diagnosis in a patient with a reactive lipoidal test (fluorescent treponemal antibody–absorbed, *T. pallidum* particle agglutination, enzyme immunoassay/chemiluminescence immunoassay).

III-168. The answer is A. *(Chap. 177)* The patient in question III-167 has findings and lab studies consistent with neurosyphilis. Penicillin G benzathine, even at high doses, does not produce treponemicidal concentrations of penicillin G in cerebrospinal fluid (CSF) and should not be used for treatment of neurosyphilis. Asymptomatic neurosyphilis may relapse as symptomatic disease after treatment with benzathine penicillin, and the risk of relapse may be higher in HIV-infected patients. Both symptomatic and asymptomatic neurosyphilis should be treated with aqueous penicillin (Table III-168). Administration either of IV aqueous crystalline penicillin G or of IM aqueous procaine penicillin G plus oral probenecid in recommended doses is thought to ensure treponemicidal concentrations of penicillin G in CSF. The clinical response to penicillin therapy for meningeal syphilis is dramatic, but treatment of neurosyphilis with existing parenchymal damage may only arrest disease progression. No data suggest that additional therapy (e.g., penicillin G benzathine for 3 weeks) is beneficial after treatment for neurosyphilis. The use of antibiotics other than penicillin G for the treatment of neurosyphilis has not been studied, although limited data suggest that ceftriaxone may be used. In patients with confirmed penicillin allergy, desensitization and treatment with penicillin are recommended. Although early syphilis (primary syphilis, secondary syphilis without neurologic involvement, and early latent syphilis) is effectively treated with a single dose of IM benzathine penicillin G, and late latent, cardiovascular, or benign tertiary syphilis are effectively treated with three weekly doses of IM benzathine penicillin G, this does not produce detectable concentrations of penicillin in the CSF. It is not recommended for the treatment of neurosyphilis.

TABLE III-168 Recommendations for the Treatment of Syphilis[a]

Stage of Syphilis	Patients without Penicillin Allergy	Patients with Confirmed Penicillin Allergy
Primary, secondary, or early latent	*CSF normal or not examined:* Penicillin G benzathine (single dose of 2.4 mU IM) *CSF abnormal:* Treat as neurosyphilis.	*CSF normal or not examined:* Tetracycline HCl (500 mg PO qid) or doxycycline (100 mg PO bid) for 2 weeks *CSF abnormal:* Treat as neurosyphilis.
Late latent (or latent of unknown duration), cardiovascular, or benign tertiary	*CSF normal or not examined:* Penicillin G benzathine (2.4 mU IM weekly for 3 weeks) *CSF abnormal:* Treat as neurosyphilis.	*CSF normal and patient not infected with HIV:* Tetracycline HCl (500 mg PO qid) or doxycycline (100 mg PO bid) for 4 weeks *CSF normal and patient infected with HIV:* Desensitize and treat with penicillin if compliance cannot be ensured. *CSF abnormal:* Treat as neurosyphilis.
Neurosyphilis (asymptomatic or symptomatic)	Aqueous crystalline penicillin G (18–24 mU/d IV, given as 3–4 mU q4h or continuous infusion) for 10–14 days *or* Aqueous procaine penicillin G (2.4 mU/d IM) plus oral probenecid (500 mg qid), both for 10–14 days	Desensitize and treat with penicillin.
Syphilis in pregnancy	According to stage	Desensitize and treat with penicillin.

[a] See text for indications for CSF examination.

Abbreviations: CSF, cerebrospinal fluid; IM, intramuscularly; mU, million units.

Source: Adapted with permission from the 2015 Sexually Transmitted Diseases Treatment Guidelines from the Centers for Disease Control and Prevention.

III-169. The answer is B. *(Chap. 177)* Neurosyphilis can occur at any stage of syphilis (early or late). The incidence of neurosyphilis is higher in those co-infected with HIV and in those with high titer nontreponemal antibody tests. Indications for CSF fluid examination in adults with syphilis include signs or symptoms of nervous system involvement (e.g., meningitis, hearing loss, cranial nerve palsies, altered mental status, ophthalmic disease, ataxia), RPR or VDRL titer ≥1:32, active tertiary syphilis, or suspected treatment failure (Table III-169). In addition, patients with HIV, especially with CD4+ T-cell count ≤350/μL, should undergo CSF examination. Otherwise, CSF examination is not routinely recommended in primary or secondary syphilis absent neurologic signs or symptoms.

TABLE III-169 Indications for Cerebrospinal Fluid Examination in Adults with All Stages of Syphilis

All Patients
Signs or symptoms of nervous system involvement (e.g., meningitis, hearing loss, cranial nerve dysfunction, altered mental status, ophthalmic disease [e.g., uveitis, iritis, pupillary abnormalities], ataxia, loss of vibration sense), *or* RPR or VDRL titer ≥1:32, *or* Active tertiary syphilis, *or* Suspected treatment failure
Additional Indications in HIV-Infected Persons
CD4+ T-cell count ≤350/μL, *or* All HIV-infected persons (recommended by some experts)

Abbreviations: RPR, rapid plasma reagin; VDRL, Venereal Disease Research Laboratory.
Source: Adapted with permission from the 2010 Sexually Transmitted Diseases Treatment Guidelines from the Centers for Disease Control and Prevention.

III-170. The answer is A. *(Chap. 178)* This patient has yaws, a treponemal infection. Also known as *pian*, *framboesia*, or *bouba*, yaws is characterized by the development of one or several primary lesions ("mother yaw") followed by multiple disseminated skin lesions. All early skin lesions are infectious and may persist for many months; cutaneous relapses are common during the first 5 years. Late manifestations, affecting ~10% of untreated persons, are destructive lesions of skin, bone, and joints. The infection is transmitted by direct contact with infectious lesions, often during play or group sleeping, and may be enhanced by disruption of the skin by insect bites or abrasions. Although *Treponema pallidum* subspecies *pertenue* DNA has been detected on flies and fomites from endemic regions, there is no convincing evidence of insect or fomite transmission of infection. After an average of 3–4 weeks, the first lesion begins as a papule—usually on an extremity—and then enlarges (particularly during moist warm weather) to become ulcerated or papillomatous ("raspberry-like"—thus the name framboesia). Regional lymphadenopathy develops, and the lesion usually heals within 6 months; dissemination is thought to occur during the early weeks of infection. A generalized secondary eruption, accompanied by generalized lymphadenopathy, appears either concurrent with or after the primary lesion; may take several forms—macular, papular, or papillomatous; and may become secondarily infected with other bacteria, including *Haemophilus ducreyi*. Painful papillomatous lesions on the soles of the feet result in a crablike gait ("crab yaws"), and periostitis may result in nocturnal bone pain and polydactylitis. The current World Health Organization-recommended therapy for patients and their contacts includes either azithromycin (30 mg/kg, up to a maximum of 2 g) or benzathine penicillin G (1.2 million units IM for adults; 600,000 units for children <10 years old); these two drugs have been shown to be equivalent in a recent study. The recommended dose of benzathine penicillin is half of that recommended for early venereal syphilis, and no controlled efficacy studies have been conducted. Definitive evidence of resistance to penicillin is lacking, although relapsing lesions have been reported after penicillin treatment in Papua New Guinea. Rifampin, isoniazid, pyrazinamide, and ethambutol are used to treat tuberculosis. Dapsone and rifampicin are used to treat leprosy. Vancomycin is a broad-spectrum antibiotic that can treat many gram-positive infections. Piperacillin-tazobactam is a very broad-spectrum extended-spectrum penicillin with a β-lactamase inhibitor used to treat many gram-positive as well as many gram-negative infections.

III-171. The answer is C. *(Chap. 179)* The clinical triad of hemorrhage, jaundice, and acute kidney injury caused by pathogenic *Leptospira* infection is eponymously known as Weil syndrome. *Leptospira* affect most mammalian species, but rats are an important reservoir. The organism may establish a symbiotic relationship with the host to persist in the urogenital tract for years. Water is a similarly important vehicle for the transmission of disease. Leptospirosis has been recognized in deteriorating inner cities with expanding rat populations. Disease ranges in severity from a mild illness that never comes to medical attention to rapidly progressive and severe illness with case fatality rates as high as 50%. In the leptospiremic phase of illness, leptospires disseminate hematogenously to vital organs. Hemorrhagic complications may involve the lungs, gastrointestinal tract, urogenital tract, or skin and are often associated with thrombocytopenia. Jaundice is common, but widespread hepatic necrosis is not. The kidneys are invariably involved. Renal involvement includes acute tubular damage and interstitial nephritis, and a nonoliguric hypokalemic renal injury is characteristic of early leptospirosis. Deregulation of several transporters along the nephron (e.g., NKCC2, NHE1, Na/K ATPase, AQP1, AQP2) contribute to tubular electrolyte wasting and lead to hypokalemia and hyponatremia. Wasting of magnesium in the urine is also common in leptospiral nephropathy.

III-172. The answer is E. *(Chap. 180)* The smear shows a tick-borne relapsing fever (TBRF) spirochete (*Borrelia turicatae*) in the center of the field. In North America, TBRF occurs as single cases or small case clusters through transient exposure of persons to infested buildings or caves in less populated areas where the rodent reservoirs have nests. The soft tick vectors typically feed for no more than 30 minutes, usually while the victim is sleeping. Relapsing fever presents with the sudden onset of fever. Febrile periods are punctuated by intervening afebrile periods of a few days; this pattern occurs at least twice. The patient's temperature is ≥39°C and may be as high as 43°C. The first fever episode often ends in a crisis lasting ~15–30 minutes and consisting of rigors, a further elevation in temperature, and increases in pulse and blood pressure. The crisis phase is followed by profuse diaphoresis, falling temperature, and hypotension, which usually persist for several hours. In TBRF, multiple febrile periods last 1–3 days each. In both forms, the interval between fevers ranges from 4 to 14 days, sometimes with symptoms of malaise and fatigue. The symptoms that accompany the fevers are usually nonspecific. Headache, neck stiffness, arthralgia, myalgia, and nausea may accompany the first and subsequent febrile episodes. An enlarging spleen and liver cause abdominal pain. In North America, *B. turicatae* infection has neurologic manifestations more often than *B. hermsii* infection. Meningoencephalitis can result in residual hemiplegia or aphasia. Myelitis and radiculopathy may develop. The bedrock for laboratory diagnosis remains what it has been for a century: direct detection of the spirochetes by microscopy of the blood. Manual differential counts of white blood cells by Wright or Giemsa stain usually reveal spirochetes in thin blood smears if their concentration is ≥105/mL and several oil-immersion fields are examined.

Brucellosis typically presents after drinking raw milk or other dairy products, which this patient did not endorse. Colorado tick fever is a viral disease spread by Rocky Mountain wood ticks in the western United States. The pattern of fever is slightly different from TBRF as the cycle is 2–3 days of fever followed by 2–3 days of normal temperature. Leptospirosis often has two phases of fever. The first occurs during the acute infection, lasting 7–10 days. In some individuals, the fever will recur 3–10 days later during the immune phase. The typical route of infection is prolonged contact with infected rodent droppings in wet environments. Lymphocytic choriomeningitis is a viral infection that is most commonly transmitted via contact with urine or droppings from the common house mouse. This illness usually has two phases as well. During the first phase, which occurs 8–13 days after exposure, an individual will experience fevers, malaise, and myalgias. In the second phase of illness, symptoms more typical of meningitis occur.

III-173. The answer is C. *(Chap. 181)* The picture shows the characteristic rash of erythema migrans, the defining lesion of Lyme disease caused by *Borrelia burgdorferi*. Erythema migrans appears at the site of the tick bite within 3–32 days following the initial bite. It typically begins as a red macule or papule and expands slowly to form an annular lesion. As the lesion gets larger, the classic targetoid appearance develops with a bright red outer ring as well as ongoing erythema at the central lesion with clearing in between. The most common sites of erythema migrans are the classic locations of tick bites, including the groin, axilla, and thigh. The presence of this lesion in an endemic area for Lyme disease is an indication for treatment and does not require serologic confirmation. *Anaplasma phagocytophilum* is the causative organism of human granulocytic anaplasmosis. This rickettsial disease is also transmitted through a tick bite and is prevalent in the upper Midwest, New England, parts of the Mid-Atlantic, and northern California. Rash occurs in about 6% of cases, although no specific rash is identified. The most common manifestations are fevers, malaise, and myalgia. *Bartonella henselae* (option B) is the organism responsible for cat-scratch fever, which can present with mild erythema near the site of the injury and markedly enlarged lymph nodes. *Ehrlichia chaffeensis* is another rickettsial organism that is transmitted by the bite of a tick and is common in the southeast, northeast, Texas, and California. Human monocytic ehrlichiosis is the disease caused by the organism and presents with nonspecific symptoms of fever, malaise, and myalgia. Rash is also not common in ehrlichiosis. *Rickettsia rickettsii* is the rickettsial organism responsible for Rocky Mountain spotted fever (RMSF). About 90% of individuals with RMSF have a rash during the course of the illness. The rash most commonly presents with diffuse macules beginning on the wrists and ankles and spreading to the trunk.

III-174. The answer is C. *(Chap. 181)* Within several weeks after the onset of illness, ~8% of patients with Lyme disease develop cardiac involvement. The most common abnormality is a fluctuating degree of atrioventricular block (first-degree, Wenckebach, or complete heart block). Some patients have more diffuse cardiac involvement, including electrocardiographic changes indicative of acute myopericarditis, left ventricular dysfunction evident on radionuclide scans, or (in rare cases) cardiomegaly or fatal pancarditis. Cardiac involvement lasts for only a few weeks in most patients but may recur in untreated patients. Acute myocardial infarction can cause complete heart block, particularly in the event of an inferior myocardial infarction. However, this patient has minimal risk factors for cardiac disease, is otherwise healthy, and has no symptoms to suggest this as a cause. Chagas disease is caused by *Trypanosoma cruzi*, a parasite endemic to Mexico and Central and South America. Sarcoidosis is a systemic disease that pathologically demonstrates the diffuse presence of noncaseating granulomas in a variety of tissues. Conduction abnormalities including complete heart block and ventricular tachycardia can be the presenting symptoms of the disease. More commonly, sarcoidosis would have pulmonary manifestations. While sarcoidosis is certainly possible, it would be a diagnosis of exclusion as his risk factors make Lyme disease more likely. Subacute bacterial endocarditis can also result in complete heart block if the endocarditis progresses to develop a valve ring abscess. The patient with bacterial endocarditis would present with a more acute illness, with fevers, weight loss, and a murmur on examination.

III-175. The answer is A. *(Chap. 181)* Lyme serology tests should be done only in patients with an intermediate pretest probability of having Lyme disease (Table III-175). The presence of erythema migrans in patients in options B and E is diagnostic of Lyme disease in the correct epidemiologic context. The diagnosis in these cases is entirely clinical and no serologic testing is required. The clinical course of the patient in option C sounds more consistent with systemic lupus erythematosus, and initial laboratory evaluation should focus on this diagnosis. Patients with chronic fatigue, myalgias, and cognitive change are occasionally concerned about Lyme disease as a potential etiology for their symptoms. However, the pretest probability of Lyme is low in these patients, assuming the absence of antecedent erythema migrans, and a positive serology is unlikely to be a true positive test. Lyme arthritis typically occurs months after the initial infection and occurs in approximately 60% of untreated patients. The typical attack is large joint, oligoarticular, and intermittent, lasting weeks at a time. Oligoarticular arthritis carries a broad differential diagnosis including sarcoidosis, spondyloarthropathy, rheumatoid arthritis, psoriatic

TABLE III-175 Algorithm for Testing for and Treating Lyme Disease

Pretest Probability	Example	Recommendation
High	Patients with erythema migrans	Empirical antibiotic treatment without serologic testing
Intermediate	Patients with oligoarticular arthritis	Serologic testing and antibiotic treatment if test results are positive
Low	Patients with nonspecific symptoms (myalgias, arthralgias, fatigue)	Neither serologic testing nor antibiotic treatment

Source: Data from Nichol G et al: Test-treatment strategies for patients suspected of having Lyme disease: a cost-effectiveness analysis. *Ann Intern Med* 128:37, 1998.

arthritis, and Lyme disease. Lyme serology is appropriate in this situation. Patients with Lyme arthritis usually have the highest IgG antibody responses seen in the infection.

III-176. and III-177. **The answers are B and D, respectively.** *(Chap. 181)* This patient has Lyme disease, due to *Borrelia burgdorferi*. Partial central clearing, a bright red border, and a target center are very suggestive of this erythema migrans (EM) lesion. The fact that multiple lesions exist implies disseminated infection, rather than a primary tick bite inoculation where only one lesion is present. Potential complications of secondary Lyme disease in the United States include migratory arthritis, meningitis, cranial neuritis, mononeuritis multiplex, myelitis, varying degrees of atrioventricular block, and, less commonly, myopericarditis, splenomegaly, and hepatitis. Skin involvement is commonly accompanied by severe headache, mild stiffness of the neck, fever, chills, migratory musculoskeletal pain, arthralgias, and profound malaise and fatigue. Less common manifestations include generalized lymphadenopathy or splenomegaly, hepatitis, sore throat, nonproductive cough, conjunctivitis, iritis, or testicular swelling. Symptoms suggestive of meningeal irritation may develop early in Lyme disease when EM is present but usually are not associated with cerebrospinal fluid (CSF) pleocytosis or an objective neurologic deficit.

After several weeks or months, ~15% of untreated patients develop frank neurologic abnormalities, including meningitis, subtle encephalitic signs, cranial neuritis (including bilateral facial palsy), motor or sensory radiculoneuropathy, peripheral neuropathy, mononeuritis multiplex, cerebellar ataxia, or myelitis—alone or in various combinations. In children, the optic nerve may be affected because of inflammation or increased intracranial pressure, and these effects may lead to blindness. In the United States, the usual pattern consists of fluctuating symptoms of meningitis accompanied by facial palsy and peripheral radiculoneuropathy. Lymphocytic pleocytosis (~100 cells/μL) is found in CSF, often along with elevated protein levels and normal or slightly low glucose concentrations. Within several weeks after the onset of illness, ~8% of patients develop cardiac involvement. The most common abnormality is a fluctuating degree of atrioventricular block (first-degree, Wenckebach, or complete heart block). Months after the onset of infection, ~60% of patients in the United States who have received no antibiotic treatment develop frank arthritis. The typical pattern comprises intermittent attacks of oligoarticular arthritis in large joints (especially the knees), lasting for weeks or months in a given joint. Although rare, chronic neurologic involvement also may become apparent from months to several years after the onset of infection, sometimes after long periods of latent infection. The most common form of chronic central nervous system involvement is subtle encephalopathy affecting memory, mood, or sleep, and the most common form of peripheral neuropathy is an axonal polyneuropathy manifested as either distal paresthesia or spinal radicular pain. Patients with encephalopathy frequently have evidence of memory impairment in neuropsychological tests and abnormal results in CSF analyses. Acute Lyme disease involving the skin and/or joints is treated with oral doxycycline unless the patient is pregnant or <9 years old. Amoxicillin and macrolides (azithromycin) are less effective therapies. Ceftriaxone is indicated for acute disease in the presence of nervous system involvement (meningitis, facial palsy, encephalopathy, radiculoneuritis) or third-degree heart block. It may also be used for treatment of patients with arthritis who do not respond to oral therapy. First-generation cephalosporins are not active against *B. burgdorferi*. While the rash of EM may look like cellulitis due to staphylococci or streptococci, there is no proven efficacy of vancomycin for Lyme disease.

III-178. The answer is B. *(Chap. 182)* The clinical history and the blood smear are consistent with human granulocytotropic anaplasmosis (HGA) due to *Anaplasma phagocytophilum*. On the smear a neutrophil contains two morulae vacuoles filled with *A. phagocytophilum*. The global geographic distribution of HGA is similar to that of Lyme disease because they share *Ixodes* tick vectors. Natural reservoirs for *A. phagocytophilum* are white-footed mice, squirrels, and white-tailed deer in the United States and red deer in Europe. HGA incidence peaks in May through July, but the disease can occur throughout the year with exposure to *Ixodes* ticks. HGA often affects males (59%) and older persons (median age, 51 years). Seroprevalence rates are high in endemic regions; thus it seems likely that most individuals develop subclinical infections. The incubation period for HGA is 4–8 days, after which the disease manifests as fever (75–100% of cases), myalgia (75%), headache (83%), and malaise (97%). A minority of patients develop nausea, vomiting, or diarrhea (21–39%); cough (29%); or confusion (17%). A rash in HGA (6%) almost invariably reflects co-infection with *Borrelia*, resulting in erythema migrans. Most patients develop thrombocytopenia (79%) and/or leukopenia (60%) with increased serum hepatic aminotransferase levels (91%). Life-threatening complications occur most often in the elderly and include renal failure, adult respiratory distress syndrome, a toxic shock–like syndrome, pneumonia, and a disseminated intravascular coagulation– or sepsis-like syndrome. Peripheral-blood film examination for neutrophil morulae can yield a diagnosis in 20–75% of infections. Polymerase chain reaction testing of blood from patients with active disease before doxycycline therapy is sensitive and specific. Serodiagnosis is retrospective, requiring a fourfold increase in *A. phagocytophilum* antibody titer (to ≥160) in paired serum samples obtained 1 month apart. Since seroprevalence is high in some regions, a single acute-phase titer should not be used for diagnosis. Doxycycline 100 mg PO bid is the treatment of choice.

III-179. The answer is B. *(Chap. 182)* This patient demonstrates evidence of Rocky Mountain spotted fever (RMSF), which has progressed over the course of several days due to lack of initial recognition and treatment. RMSF is caused by infection with *Rickettsia rickettsii* and is transmitted through the bite of an infected dog tick. RMSF has been diagnosed in 47 states and is most commonly diagnosed in the south-central and southeastern states. Symptoms typically begin about 1 week following inoculation. The initial symptoms are vague and are easily misdiagnosed as a viral infection with fever, myalgias, malaise, and headache predominating. Although almost all patients with RMSF develop a rash during the course of the illness, rash is present in only 14% on the first day, and the lack of rash in a patient who is at risk for RMSF should not delay treatment. By day 3, 49% of individuals develop a rash. The rash initially is a macular rash that begins on the wrists and ankles and progresses to involve the extremities and trunk. Over time, hemorrhaging into the macules occurs and has a petechial appearance. As the illness progresses, respiratory failure and central nervous system (CNS) manifestations can develop. Encephalitis, presenting as confusion and lethargy, is present about 25% of the time. Other manifestations can include renal failure, hepatic injury, and anemia. Treatment for RMSF is doxycycline 100 mg twice daily. It can be administered orally or intravenously. As this patient shows progressive disease with CNS involvement, hospital admission for treatment is warranted to monitor for further decompensation in the patient's condition. If the patient were more clinically stable, outpatient therapy would be appropriate. Treatment should not be delayed while awaiting confirmatory serologic testing as untreated cases of RMSF are fatal, usually within 8–15 days. Treatment with any sulfa drugs should be avoided as the drug is ineffective and can worsen the disease course. IV ceftriaxone and vancomycin are appropriate agents for bacterial meningitis. Although this could be a consideration in this patient with fever, confusion, and a rash, meningococcemia would present with a more fulminant course, and the patient's risk factor (hiking in an endemic area) would make RMSF more likely.

III-180. The answer is D. *(Chap. 183)* This patient presents with symptoms of atypical pneumonia, and the most common causative organism for atypical pneumonia is *Mycoplasma pneumoniae*. Pneumonia caused by *Mycoplasma* occurs worldwide without a specific seasonal preference. *M. pneumoniae* is a highly infectious organism and is spread by respiratory droplets. It is estimated that approximately 80% of individuals within the same

TABLE III-180 Diagnostic Tests for Respiratory *Mycoplasma pneumoniae* Infection[a]

Test	Sensitivity (%)	Specificity (%)
Respiratory culture	≤60	100
Respiratory PCR	65–90	90–100
Serologic studies[b]	55–100	55–100

[a] A combination of PCR and serology is suggested for routine diagnosis. If macrolide resistance is suspected, resistance testing by culture and/or PCR is available.

[b] Acute- and convalescent-phase serum samples are recommended.

Abbreviation: PCR, polymerase chain reaction.

family will experience the infection once one person becomes infected. Outbreaks of *M. pneumoniae* also occur in institutional settings, including boarding schools and military bases. Clinical manifestations of *M. pneumoniae* typically are pharyngitis, tracheobronchitis, wheezing, or nonspecific upper respiratory syndrome. Although many commonly believe the organism is associated with otitis media and bullous myringitis, there are little clinical data to support this assertion. Atypical pneumonia occurs in less than 15% of individuals infected with *M. pneumoniae*. The onset of pneumonia is typically gradual with preceding symptoms of upper respiratory infection. Cough is present and, although often extensive, is typically nonproductive. Examination typically demonstrates wheezing or rales in approximately 80% of patients. The most common x-ray findings are bilateral peribronchial pneumonia with increased interstitial markings. Lobar consolidation is uncommon. Definitive diagnosis requires demonstration of *M. pneumoniae* nucleic acids on polymerase chain reaction of respiratory secretions or performance of serologic testing (Table III-180). Often, however, the patients are treated empirically without obtaining a definitive diagnosis. Other causes of atypical pneumonia are *Chlamydophila pneumoniae* and *Legionella pneumophila*. *C. pneumoniae* more commonly causes pneumonia in school-aged children, although adults can become reinfected. *Legionella* pneumonia is often associated with outbreaks of disease due to contaminated water supplies. Individuals with *Legionella* pneumonia can become quite sick and develop respiratory failure. Adenovirus is a common viral cause of upper respiratory tract infection and has been associated with outbreaks of pneumonia among military recruits and in colleges. *Streptococcus pneumoniae* is the most common cause of community-acquired pneumonia, but typically presents with radiographic lobar or segmental consolidation.

III-181. The answer is E. *(Chap. 183)* In many episodes of *Chlamydia*-negative nongonococcal urethritis, ureaplasmas may be the causative agent. These organisms may also cause chronic voiding symptoms in women. The common presence of ureaplasmas in the urethra of asymptomatic men may suggest either that only certain serovars are pathogenic or that predisposing factors, such as lack of immunity, must exist in persons who develop symptomatic infection. Alternatively, disease may develop only on initial exposure to ureaplasmas. Ureaplasmas have been implicated in epididymitis. *Mycoplasma genitalium* also appears to cause urethritis. Herpes simplex virus (HSV)-1 and HSV-2 can cause urethritis, but typically has other symptoms as well, particularly ulceration. *Treponema pallidum*, the causative agent of syphilis, does not tend to cause urethritis. *Chlamydia trachomatis* serovar L1 is one of the serovars that can cause lymphogranuloma venereum, which is a syndrome that does not tend to cause urethritis.

III-182. The answer is C. *(Chap. 184)* This patient is likely suffering from pneumonia due to *Chlamydia psittaci*. This organism is a relatively rare cause of pneumonia, with only about 50 confirmed cases yearly in the United States. Contrary to common belief, the organism is not limited to psittacine birds (parrots, parakeets, cockatiels, macaws), but any bird can be infected, including poultry. Most infections are seen in owners of pet birds, poultry farmers, or poultry processing workers, and outbreaks of pneumonia have been seen in poultry processing factories. Untreated psittacosis has a mortality as high as 10%. The illness presents with nonspecific symptoms of fevers, chills, myalgias, and severe headache. Gastrointestinal symptoms with hepatosplenomegaly are also common.

Severe pneumonia requiring ventilatory support can occur, and other rare manifestations include endocarditis, myocarditis, and neurologic complications. The current diagnostic tool of choice is the microimmunofluorescence test, which is a serologic test. Any titer greater than 1:16 is considered evidence of exposure to psittacosis, and paired acute and convalescent titers showing a fourfold rise in titer are consistent with psittacosis. Complement fixation tests are also used. Treatment of choice for psittacosis is tetracycline 250 mg four times daily for a minimum of 3 weeks. Public health officials should be notified to assess other workers in the factory for disease and limit exposure. Although this patient has immigrated from an area endemic for tuberculosis, she had a previous negative purified protein derivative and no known tuberculosis exposures. Her chest radiograph shows diffuse consolidation, which would not be typical for reactivation of tuberculosis. Systemic infection with *Staphylococcus aureus* from an abscess or endocarditis could present with respiratory failure related to septic emboli. However, her chest imaging is not consistent with this, and she has no risk factors (e.g., IV drug use, indwelling IV catheter) for development of *S. aureus* bloodstream infection. *Legionella pneumophila* is associated with outbreaks of disease related to contaminated water supplies or air conditioning. It should be considered in this patient in light of her ill co-workers. However, the hepatosplenomegaly is not consistent with this diagnosis. Influenza A is also a consideration for this patient, but the time of year is not consistent for seasonal influenza. In outbreaks of pandemic influenza, this would be more likely.

III-183. The answer is B. *(Chap. 184)* The patient has lymphogranuloma venereum (LGV). Primary anal or rectal infections with *Chlamydia trachomatis* have been described in women and men who have sex with men (MSM) who practice anal intercourse. In these infections, rectal involvement is initially characterized by severe anorectal pain, a bloody mucopurulent discharge, and tenesmus. LGV serovars L1, L2, and L3 have been found to cause proctitis. The LGV serovars are far more invasive and cause much more severely symptomatic disease, including severe ulcerative proctocolitis that can be clinically confused with herpes simplex virus proctitis. Histologically, LGV proctitis may resemble Crohn disease in that giant cell formation and granulomas are detected. In the United States and Europe, cases of LGV proctitis occur almost exclusively in MSM, many of whom have HIV infection. LGV begins as a small painless papule that tends to ulcerate at the site of inoculation, often escaping attention. This primary lesion heals in a few days without scarring and is usually recognized as LGV only in retrospect. LGV strains of *C. trachomatis* have occasionally been recovered from genital ulcers and from the urethra of men and the endocervix of women who present with inguinal adenopathy; these areas may be the primary sites of infection in some cases. Proctitis is more common among people who practice receptive anal intercourse, and an elevated white blood cell count in anorectal smears may predict LGV in these patients. Ulcer formation may facilitate transmission of HIV infection and other sexually transmitted and blood-borne diseases. Such patients present with anorectal pain and mucopurulent, bloody rectal discharge. The most common presenting picture in heterosexual men and women is the *inguinal syndrome*, which is characterized by painful inguinal lymphadenopathy beginning 2–6 weeks after presumed exposure. Constitutional symptoms are common during the stage of regional lymphadenopathy and, in cases of proctitis, may include fever, chills, headache, meningismus, anorexia, myalgias, and arthralgias. The inguinal adenopathy is unilateral in two-thirds of cases, and palpable enlargement of the iliac and femoral nodes is often evident on the same side as the enlarged inguinal nodes. The nodes are initially discrete, but progressive periadenitis results in a matted mass of nodes that becomes fluctuant and suppurative. Sigmoidoscopy reveals ulcerative proctitis or proctocolitis, with purulent exudate and mucosal bleeding. Histopathologic findings in the rectal mucosa include granulomas with giant cells, crypt abscesses, and extensive inflammation. These clinical, sigmoidoscopic, and histopathologic findings may closely resemble those of Crohn disease of the rectum. In this case, the nucleic acid amplification test results make the diagnosis of LGV.

III-184. The answer is A. *(Chap. 184)* This patient has pelvic inflammatory disease (PID), or salpingitis. The proportion of acute salpingitis cases caused by *Chlamydia trachomatis* varies geographically and with the population studied. It has been estimated that *C. trachomatis* causes up to 50% of PID cases in the United States. PID occurs via ascending intraluminal spread of *C. trachomatis* or *Neisseria gonorrhoeae* from the lower genital tract. Mucopurulent cervicitis is often followed by endometritis, endosalpingitis, and finally pelvic peritonitis. Her symptoms are milder. Chlamydial salpingitis produces milder symptoms than gonococcal salpingitis and may be associated with less marked adnexal tenderness. Thus, mild adnexal or uterine tenderness in a sexually active woman with cervicitis suggests chlamydial PID rather than gonococcal PID. Chronic untreated endometrial and tubal inflammation can result in tubal scarring, impaired tubal function, tubal occlusion, and infertility even among women who report no prior treatment for chlamydial infection. *C. trachomatis* has been particularly implicated in "subclinical" PID on the basis of a lack of history of PID among *Chlamydia*-seropositive women with tubal damage and detection of chlamydial DNA or antigen among asymptomatic women with tubal infertility. These data suggest that the best method to prevent PID and its sequelae is surveillance and control of lower genital tract infections along with diagnosis and treatment of sex partners and prevention of reinfections.

III-185. The answer is B. *(Chap. 185)* Relatively few viruses cause persistent or latent infections. Hepatitis B virus, hepatitis C virus (HCV), rabies virus, measles virus, HIV, human T-lymphotropic virus type 1, human papillomavirus (HPV), human herpesviruses (HHVs), and molluscum contagiosum virus (MCV) are notable exceptions. The mechanisms for persistent infection vary. HCV RNA polymerase and HIV reverse transcriptase are error prone and generate variant genomes. Genome variation can be sufficient to permit evasion of host immune responses, allowing persistent infection. HIV is also directly immunosuppressive, depleting CD4+ T lymphocytes and compromising CD8+ cytotoxic T-cell immune responsiveness. Moreover, HIV encodes the Nef protein, which downmodulates major histocompatibility complex (MHC) class I expression, rendering HIV-infected cells partially resistant to immune CD8+ T-cell lysis. HHVs establish latent infection in nonreplicating neural cells (herpes simplex virus [HSV] and varicella-zoster virus) or in replicating cells of hematopoietic lineages (Epstein-Barr virus, cytomegalovirus [CMV], HHV-6, HHV-7, and Kaposi sarcoma–associated herpesvirus [also known as HHV-8]). In their latent stage, HPV and herpesvirus genomes are largely hidden from the normal immune response. Reactivated HPV and herpesvirus infections escape immediate and effective immune responses in highly immune hosts by inhibiting host innate immune and inflammatory responses. HSV and CMV are also known to encode proteins that downregulate MHC class I expression and antigenic peptide presentation, enabling infected cells to escape recognition by and cytotoxic effects of CD8+ T lymphocytes. Rabies has been confirmed as long as 7 years after exposure. Like other poxviruses, MCV cannot establish latent infection. This virus causes persistent infection in hypertrophic skin lesions that last for months or years. MCV encodes a chemokine homologue that probably blocks inflammatory responses, an MHC class I analogue that blocks cytotoxic T lymphocyte attack, and inhibitors of cell death that prolong infected-cell viability. Hepatitis A virus does not cause persistent or latent infection.

III-186. The answer is D. *(Chap. 185)* Persistent viral infection is estimated to be the root cause of as many as 20% of human malignancies. Cancer is an accidental and highly unusual or long-term effect of oncogenic human viral infection. With most "oncogenic viruses," infection is a critical and ultimately determinative early step in carcinogenesis. Epidemiologic data firmly link hepatitis B and C virus infections to hepatocellular carcinoma. These infections elicit repetitive cycles of virus-induced liver injury followed by tissue repair and regeneration. Most cervical carcinoma and much anal carcinoma is caused by persistent infection with "high-risk" human papillomavirus type 16 or 18. Epstein-Barr virus (EBV) is the most unusual oncogenic virus in that normal B-cell infection results in latency with expression of viral proteins that can cause endless B-lymphocyte growth. Persistent EBV infection with expression of an EBV latency-associated integral membrane protein (LMP1) in latently infected epithelial cells appears to be a critical early step in the evolution of anaplastic nasopharyngeal carcinoma, a common malignancy in populations in southern China and northern Africa. EBV is also an important cause of Hodgkin lymphoma. Molecular data confirm the presence of Kaposi sarcoma–associated herpesvirus [KSHV] DNA in all Kaposi tumors, including those associated with HIV infection, transplantation, and familial transmission. KSHV infection is also etiologically implicated in pleural-effusion lymphomas and multicentric Castleman disease, which are more common among HIV-infected than among HIV-uninfected people. Herpes simplex virus is not associated with melanoma.

III-187. The answer is C. *(Chap. 187)* Herpes simplex viruses (HSV-1, HSV-2; *Herpesvirus hominis*) are DNA viruses that produce a variety of infections involving mucocutaneous surfaces, the central nervous system, and—on occasion—visceral organs. Both HSV-1 and HSV-2 are shed subclinically. Most persons infected with HSV-2 and HSV-1 have frequent subclinical bursts of reactivation lasting 2–4 hours, and the host tissue–based immune system can contain viral reactivation in the tissue before the development of clinical reactivation. Infection with HSV-1 is acquired more frequently and earlier in life than infection with HSV-2. More than 90% of adults have antibodies to HSV-1 by the fifth decade of life. In populations of low socioeconomic status, most persons acquire HSV-1 infection before the third decade of life. Many studies continue to show that both incident and—more important—prevalent HSV-2 infection enhances the acquisition rate of HIV-1. Antibodies to HSV-2 are not detected routinely until puberty. Immunocompromised patients with defects in cell-mediated immunity experience more severe and more extensive HSV infections than those with deficits in humoral immunity, such as agammaglobulinemia.

III-188. The answer is D. *(Chap. 187)* This patient has his first recurrence of symptomatic genital herpes. Short-course (1- to 3-day) regimens are preferred because of low cost, likelihood of adherence, and convenience (Table III-188). Oral acyclovir (800 mg tid for 2 days), valacyclovir (500 mg bid for 3 days), or famciclovir (750 or 1000 mg bid for 1 day, a 1500-mg single dose, or 500 mg stat followed by 250 mg q12h for 2 days) effectively shortens lesion duration. Other options include oral acyclovir (200 mg 5 times per day), valacyclovir (500 mg bid), and famciclovir (125 mg bid for 5 days). In addition, while ganciclovir is active against both HSV-1 and HSV-2, it is more toxic than acyclovir, valacyclovir, and

TABLE III-188 **Antiviral Chemotherapy for Herpes Simplex Virus Infection**

I. **Mucocutaneous HSV infections**
   A. *Infections in immunosuppressed patients*
      1. *Acute symptomatic first or recurrent episodes:* IV acyclovir (5 mg/kg q8h) or oral acyclovir (400 mg qid), famciclovir (500 mg bid or tid), or valacyclovir (500 mg bid) is effective. Treatment duration may vary from 7 to 14 days. IV therapy may be given for 2–7 days until clinical improvement and followed by oral therapy.
      2. *Suppression of reactivation disease (genital or oral–labial):* IV acyclovir (5 mg/kg q8h) or oral valacyclovir (500 mg bid) or acyclovir (400–800 mg 3–5 times per day) prevents recurrences during the 30-day period immediately after transplantation. Longer-term HSV suppression is often used for persons with continued immunosuppression. In bone marrow and renal transplant recipients, oral valacyclovir (2 g/d) is also effective in reducing cytomegalovirus infection. Oral valacyclovir at a dose of 4 g/d has been associated with thrombotic thrombocytopenic purpura after extended use in HIV-positive persons. In HIV-infected persons, oral acyclovir (400–800 mg bid), valacyclovir (500 mg bid), or famciclovir (500 mg bid) is effective in reducing clinical and subclinical reactivations of HSV-1 and HSV-2.
   B. *Infections in immunocompetent patients*
      1. *Genital herpes*
         a. *First episodes:* Oral acyclovir (200 mg 5 times per day or 400 mg tid), valacyclovir (1 g bid), or famciclovir (250 mg bid) for 7–14 days is effective. IV acyclovir (5 mg/kg q8h for 5 days) is given for severe disease or neurologic complications such as aseptic meningitis.
         b. *Symptomatic recurrent genital herpes:* Short-course (1- to 3-day) regimens are preferred because of low cost, likelihood of adherence, and convenience. Oral acyclovir (800 mg tid for 2 days), valacyclovir (500 mg bid for 3 days), or famciclovir (750 or 1000 mg bid for 1 day, a 1500-mg single dose, or 500 mg stat followed by 250 mg q12h for 2 days) effectively shortens lesion duration. Other options include oral acyclovir (200 mg 5 times per day), valacyclovir (500 mg bid), and famciclovir (125 mg bid for 5 days).
         c. *Suppression of recurrent genital herpes:* Oral acyclovir (400–800 mg bid) or valacyclovir (500 mg daily) is given. Patients with >9 episodes per year should take oral valacyclovir (1 g daily or 500 mg bid) or famciclovir (250 mg bid or 500 mg bid).

(*continued*)

TABLE III-188 Antiviral Chemotherapy for Herpes Simplex Virus Infection (*Continued*)

2. *Oral–labial HSV infections*
    a. *First episode:* Oral acyclovir is given (200 mg 5 times per day or 400 mg tid); an oral acyclovir suspension can be used (600 mg/m^2 qid). Oral famciclovir (250 mg bid) or valacyclovir (1 g bid) has been used clinically. The duration of therapy is 5–10 days.
    b. *Recurrent episodes:* If initiated at the onset of the prodrome, single-dose or 1-day therapy effectively reduces pain and speeds healing. Regimens include oral famciclovir (a 1500-mg single dose or 750 mg bid for 1 day) or valacyclovir (a 2-g single dose or 2 g bid for 1 day). Self-initiated therapy with 6-times-daily topical penciclovir cream effectively speeds healing of oral–labial HSV infection. Topical acyclovir cream has also been shown to speed healing.
    c. *Suppression of reactivation of oral–labial HSV:* If started before exposure and continued for the duration of exposure (usually 5–10 days), oral acyclovir (400 mg bid) prevents reactivation of recurrent oral–labial HSV infection associated with severe sun exposure.
3. *Surgical prophylaxis of oral or genital HSV infection:* Several surgical procedures, such as laser skin resurfacing, trigeminal nerve-root decompression, and lumbar disk surgery, have been associated with HSV reactivation. IV acyclovir (3–5 mg/kg q8h) or oral acyclovir (800 mg bid), valacyclovir (500 mg bid), or famciclovir (250 mg bid) effectively reduces reactivation. Therapy should be initiated 48 hours before surgery and continued for 3–7 days.
4. *Herpetic whitlow:* Oral acyclovir (200 mg) is given 5 times daily (alternative: 400 mg tid) for 7–10 days.
5. *HSV proctitis:* Oral acyclovir (400 mg 5 times per day) is useful in shortening the course of infection. In immunosuppressed patients or in patients with severe infection, IV acyclovir (5 mg/kg q8h) may be useful.
6. *Herpetic eye infections:* In acute keratitis, topical trifluorothymidine, vidarabine, idoxuridine, acyclovir, penciclovir, and interferon are all beneficial. Debridement may be required. Topical steroids may worsen disease.

II. Central nervous system HSV infections
- A. *HSV encephalitis:* IV acyclovir (10 mg/kg q8h; 30 mg/kg per day) is given for 10 days or until HSV DNA is no longer detected in cerebrospinal fluid.
- B. *HSV aseptic meningitis:* No studies of systemic antiviral chemotherapy exist. If therapy is to be given, IV acyclovir (15–30 mg/kg per day) should be used.
- C. *Autonomic radiculopathy:* No studies are available. Most authorities recommend a trial of IV acyclovir.

III. Neonatal HSV infections: IV acyclovir (60 mg/kg per day, divided into 3 doses) is given. The recommended duration of IV treatment is 21 days. Monitoring for relapse should be undertaken. Continued suppression with oral acyclovir suspension should be given for 3–4 months.

IV. Visceral HSV infections
- A. *HSV esophagitis:* IV acyclovir (15 mg/kg per day) is given. In some patients with milder forms of immunosuppression, oral therapy with valacyclovir or famciclovir is effective.
- B. *HSV pneumonitis:* No controlled studies exist. IV acyclovir (15 mg/kg per day) should be considered.

V. Disseminated HSV infections: No controlled studies exist. IV acyclovir (5 mg/kg q8h) should be tried. Adjustments for renal insufficiency may be needed. No definite evidence indicates that therapy will decrease the risk of death.

VI. Erythema multiforme associated with HSV: Anecdotal observations suggest that oral acyclovir (400 mg bid or tid) or valacyclovir (500 mg bid) will suppress erythema multiforme.

VII. Infections due to acyclovir-resistant HSV: IV foscarnet (40 mg/kg IV q8h) should be given until lesions heal. The optimal duration of therapy and the usefulness of its continuation to suppress lesions are unclear. Some patients may benefit from cutaneous application of trifluorothymidine or 1% cidofovir gel, both of which must be compounded at a pharmacy. These preparations should be applied once daily for 5–7 days. Topical imiquimod can be considered. The helicase primase inhibitor pritelivir is being studied for treatment of acyclovir-resistant HSV infection. IV cidofovir (5 mg/kg weekly) may be considered.

VIII. Acyclovir and pregnancy: No adverse effects to the fetus or newborn have been attributable to acyclovir. Acyclovir can be used in all stages of pregnancy and among women who are breastfeeding (the drug can be found in breast milk). Suppressive acyclovir treatment in late pregnancy reduces the frequency of cesarean delivery among women with recurrent genital herpes. Such treatment may not protect against transmission to neonates.

famciclovir and generally is not recommended for the treatment of HSV infections. Anecdotal case reports suggest that ganciclovir may also be less effective than acyclovir for the treatment of HSV infections. All three recommended compounds—acyclovir, valacyclovir, and famciclovir—have proved effective in shortening the duration of symptoms and lesions of mucocutaneous HSV infections in both immunocompromised and immunocompetent patients.

III-189. **The answer is C.** *(Chap. 187)* Herpes encephalitis accounts for 10–20% of sporadic cases of viral encephalitis in the United States. It most commonly occurs in patients aged 5–30 and >50 years old. Herpes simplex virus (HSV)-1 accounts for >95% of cases, and most adults have clinical or serologic evidence of HSV-1 mucocutaneous infection before onset of central nervous system symptoms. HSV encephalitis is characterized by the acute onset of fever and focal neurologic signs, particularly in the temporal lobe. Electroencephalogram (EEG) abnormalities in the temporal lobe are common. Cerebrospinal fluid (CSF) will show elevated protein, lymphocyte leukocytosis with red cells, and normal glucose. HSV polymerase chain reaction testing of CSF is highly sensitive and specific for diagnosis. Treatment with acyclovir reduces mortality; however, neurologic sequelae are common, particularly in older patients. Differentiation of HSV encephalitis from other viral forms is difficult. Most experts recommend initiation of empiric acyclovir in any patient with suspected encephalitis pending a confirmed or alternative diagnosis. Tuberculosis meningitis presents typically as a basilar meningitis and not encephalitis. The history, clinical findings, EEG abnormalities, and radiologic findings make fungal meningitis unlikely. CSF oligoclonal bands are typically seen in patient with multiple sclerosis.

III-190. **The answer is C.** (*Chap. 188,* https://www.cdc.gov/mmwr/volumes/67/wr/mm6703a5.htm, https://www.cdc.gov/vaccines/vpd/shingles/hcp/shingrix/recommendations.html) The Centers for Disease Control and Prevention (CDC) recommends Shingrix (recombinant zoster vaccine) as preferred over Zostavax® (zoster vaccine live) for the prevention of herpes zoster (shingles) and related complications. The CDC recommends two doses of Shingrix separated by 2 to 6 months for immunocompetent adults aged 50 years and older, whether or not they report a prior episode of herpes zoster, and whether or not they report a prior dose of Zostavax. Of note, patients with chronic medical conditions (e.g., chronic renal failure, diabetes mellitus, rheumatoid arthritis, chronic pulmonary disease) who are at least 50 years of age should receive the vaccine. Shingrix can also be used for adults who are taking low-dose immunosuppressive therapy (<20 mg of prednisone daily), are anticipating immunosuppression, or have recovered from an immunocompromising illness. It is not a live vaccine so likely could be given to others who are immunocompromised, but the Advisory Committee on Immunization Practices (ACIP) has not yet released this guidance. It is not necessary to screen, either verbally or by laboratory serology, for evidence of prior varicella infection, so there is no need to screen for a history of varicella (chickenpox) infection or to conduct laboratory testing for serologic evidence of prior varicella infection. More than 99% of adults age 50 years and older worldwide have been exposed to varicella-zoster virus, and the CDC considers people born in the United States prior to 1980 immune to varicella. Therefore, even if a person does not recall having chickenpox, serologic testing for varicella immunity is not recommended. It is often a barrier to herpes zoster vaccination, and false negatives are common. However, if serologic evidence of varicella susceptibility via a negative antibody test becomes available to the health care provider, providers should follow ACIP guidelines for varicella vaccination. Shingrix has not been evaluated in persons who are seronegative to varicella, and it is not indicated for the prevention of varicella. The patient in option C should receive a varicella vaccine instead of Shingrix.

III-191. **The answer is E.** *(Chap. 188)* The hemorrhagic vesicles and pustules on an erythematous base grouped in a dermatomal distribution and with different stages of evolution are typical of varicella-zoster virus reinfection, or shingles. Patients with herpes zoster benefit from oral antiviral therapy, as evidenced by accelerated healing of lesions and resolution of zoster-associated pain with acyclovir, valacyclovir, or famciclovir. Valacyclovir and famciclovir are superior to acyclovir in terms of pharmacokinetics and pharmacodynamics and should be used preferentially. Valacyclovir, the prodrug of acyclovir, accelerates healing and resolution of zoster-associated pain more promptly than acyclovir. The dose is 1 g by mouth three times daily for 5–7 days. Ganciclovir is used to treat disseminated infection with cytomegalovirus, not varicella-zoster virus. The other agents are used to treat bacterial infections such as Lyme or *Rickettsia* (doxycycline), *Pseudomonas* (piperacillin-tazobactam), or treponemes (penicillin).

III-192. and III-193. **The answers are C and E, respectively.** *(Chap. 189)* Epstein-Barr virus (EBV) is the cause of heterophile-positive infectious mononucleosis (IM), which is characterized by fever, sore throat, lymphadenopathy, and atypical lymphocytosis. EBV is also associated with several human tumors, including nasopharyngeal carcinoma, Burkitt lymphoma, Hodgkin disease, and (in patients with immunodeficiencies) B-cell lymphoma. EBV infection occurs worldwide, with >90% of adults seropositive. In the developing world, most people are infected as young children and IM is uncommon, whereas in the more developed world, most are infected as adolescents or young adults and IM is more common. The virus is spread by contaminated saliva. Asymptomatic seropositive individuals shed the virus in saliva. In young children, the EBV infection causes mild disease with sore throat. Adolescents and young adults develop IM as described above plus often splenomegaly in the second to third week of disease. The white blood cell count is usually elevated and peaks at 10,000–20,000/μL during the second or third week of illness. Lymphocytosis is usually demonstrable, with >10% atypical lymphocytes. A morbilliform rash may occur in about 5% of patients as part of the acute illness. Most patients treated with amoxicillin develop a macular rash as pictured; this rash is not predictive of future adverse reactions to penicillins. Heterophile antibody testing will be positive in up to 40% of cases of IM in the first week of illness and up to 90% by the third week. If heterophile antibody testing is negative, the more expensive testing for IgM antibodies to viral capsid antigen is more sensitive and specific. IgG antibodies to viral capsid antigen will stay present indefinitely after initial infection and are not useful for diagnosing acute disease. Treatment of uncomplicated IM is with rest, supportive measures, and reassurance. Excessive physical activity should be avoided in the first month to avoid splenic trauma. Prednisone is not indicated and may predispose to secondary infection. It has been used at high dose when IM is complicated by airway compromise due to pharyngeal swelling, autoimmune hemolytic anemia, severe thrombocytopenia, hemophagocytic syndrome, or other severe complications. Controlled trials have shown that acyclovir has no significant impact on the course of uncomplicated IM. One study showed no benefit for combined prednisone plus acyclovir.

III-194. **The answer is D.** *(Chap. 190)* Cytomegalovirus (CMV) is an important pathogen in patients with advanced HIV infection, in whom it may cause retinitis or disseminated disease, particularly when peripheral-blood CD4+ T-cell counts fall below 50/μL. CMV retinitis is an important cause of blindness in immunocompromised patients, particularly patients with advanced AIDS. Early lesions consist of small, opaque, white areas of granular retinal necrosis that spread in a centrifugal manner and are later accompanied by hemorrhages, vessel sheathing, and retinal edema (Figure III-194). The other conditions are more common in solid organ transplant recipients. CMV is the most common viral pathogen complicating organ transplantation. In recipients of kidney, heart, lung, liver, pancreas, and vascularized composite (hand, face, other) transplants, CMV infection may result in a variety of clinical manifestations, including fever and leukopenia, hepatitis, colitis, pneumonitis, esophagitis, gastritis, and retinitis. CMV disease is an independent risk factor for both graft loss and death. Without prophylaxis, the period of maximal risk

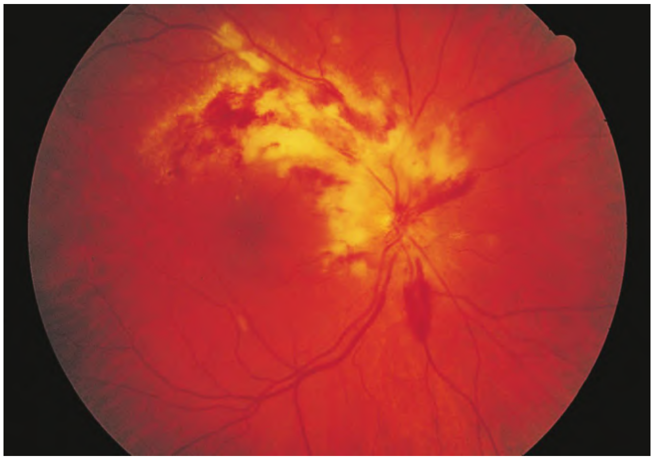


FIGURE III-194

is between 1 and 4 months after transplantation. The transplanted organ is particularly vulnerable as a target for CMV infection; thus there is a tendency for CMV hepatitis to follow liver transplantation and for CMV pneumonitis to follow lung transplantation. Syndromes produced by CMV in immunocompromised hosts ("CMV syndrome") often begin with fatigue, fever, malaise, anorexia, night sweats, and arthralgias or myalgias. Liver function abnormalities, leukopenia, thrombocytopenia, and atypical lymphocytosis may be observed during these episodes. Without treatment, CMV infection may progress to more severe end-organ disease. Gastrointestinal CMV involvement may be localized or extensive and almost exclusively affects immunocompromised hosts. Colitis is the most common clinical manifestation in organ transplant recipients.

III-195. **The answer is A.** *(Chap 190)* When the transplant donor is cytomegalovirus (CMV) IgG positive and the recipient is negative, there is a very high risk of primary CMV infection in the recipient. However, if the recipient is IgG positive, CMV occurs as a reactivation infection. When both donor and recipient are seronegative, then the risk of any CMV infection is lowest, but not zero, as a contact with an infected host could prompt primary CMV infection. Unlike nearly all other transplant patients, many donor and recipient seronegative patients do not receive chemoprophylaxis with ganciclovir. In patients who are CMV IgG negative and who received a CMV IgG–negative transplant, transfusions should be from CMV IgG–negative donors or white blood cell filtered products should be administered to reduce the risk of primary CMV infection. It is not clear whether universal prophylaxis or preemptive therapy is the preferable approach in CMV-seropositive immunocompromised hosts. Both ganciclovir and valganciclovir have been used successfully for prophylaxis and preemptive therapy in transplant recipients.

III-196. **The answer is A.** *(Chap. 190)* Human T-lymphotropic virus type 1 (HTLV-1), not human herpesvirus (HHV)-8, has been implicated in adult T-cell leukemia. All of the other conditions and presentations have been associated with HHV-8. HHV-8, which infects B lymphocytes, macrophages, and both endothelial and epithelial cells, appears to be causally related not only to Kaposi sarcoma (KS) and a subgroup of AIDS-related B-cell body cavity–based lymphomas (primary effusion lymphomas) but also to multicentric Castleman disease, a lymphoproliferative disorder of B cells. Primary HHV-8 infection in immunocompetent children may manifest as fever and maculopapular rash. Quantitative analysis of HHV-8 DNA suggests a predominance of latently infected cells in KS lesions and frequent lytic replication in multicentric Castleman disease.

III-197. **The answer is C.** *(Chap. 191)* Molluscum contagiosum virus is an obligate human pathogen that causes distinctive proliferative skin lesions. These lesions measure 2–5 mm in diameter and are pearly, flesh-colored, and umbilicated, with a characteristic dimple at the center. A relative lack of inflammation and necrosis distinguishes these proliferative lesions from other poxvirus lesions. Lesions may be found—singly or in clusters—anywhere on the body except on the palms and soles and may be associated with an eczematous rash. Molluscum contagiosum is highly prevalent among children and is the most common human disease resulting from poxvirus infection. Swimming pools are a common vector for transmission. Atopy and compromise of skin integrity increase the risk of infection. Genital lesions are more common in adults, to whom the virus may be transmitted by sexual contact. The incubation period ranges from 2 weeks to 6 months, with an average of 2–7 weeks. In most cases, the disease is self-limited and regresses spontaneously after 3–4 months in immunocompetent hosts. There are no systemic complications, but skin lesions may persist for 3–5 years. Molluscum contagiosum can be associated with immunosuppression and is frequently seen among HIV-infected patients. The disease can be more generalized, severe, and persistent in AIDS patients than in other groups. Moreover, molluscum contagiosum can be exacerbated in the immune reconstitution inflammatory syndrome associated with the initiation of antiretroviral therapy. The diagnosis of molluscum contagiosum is typically based on its clinical presentation. Herpes simplex virus lesions are typically painful and ulcerated. Varicella zoster lesions are also typically painful and do not present as "papules." Human papillomavirus and syphilis may present with a single or multiple papules, but they do not have the characteristic umbilicated appearance.

III-198. The answer is D. *(Chap. 192)* The most likely diagnosis based on her antecedent illness with a facial rash is parvovirus infection. Arthropathy is uncommon in childhood parvovirus infection but may cause a diffuse symmetric arthritis in up to 50% of adults. This corresponds to the immune phase of illness when IgM antibodies are developed. The arthropathy syndrome is more common in women than men. The distribution of affected joints is typically symmetric, most commonly in the small joints of the hands and less commonly the ankles, knees, and wrists. Occasionally, the arthritis persists over months and can mimic rheumatoid arthritis. Rheumatoid factor can be detected in serum. Parvovirus B19V infection may trigger rheumatoid disease in some patients and has been associated with juvenile idiopathic arthritis. Reactive arthritis due to *Chlamydia* or a list of other bacterial pathogens tends to affect large joints such as the sacroiliac joints and spine. It is also sometimes accompanied by uveitis and urethritis. The large number of joints involved with a symmetric distribution argues against crystal or septic arthropathy.

III-199. The answer is E. *(Chap. 193)* The development of human papillomavirus (HPV) vaccines effective in preventing infection and HPV-associated disease represents a major development in the last 15 years. The vaccines use virus-like particles (VLPs) that consist of the HPV L1 major capsid protein. The L1 protein self-assembles into VLPs when expressed in eukaryotic cells (i.e., yeast for the Merck vaccine or insect cells for the GlaxoSmithKline vaccine). These VLPs contain the same epitopes as the HPV virion. However, they do not contain genetic material and cannot transmit infection. The bivalent L1 VLP vaccine (HPV types 16 and 18) marketed under the name Cervarix (GlaxoSmithKline) is administered by IM injection at months 0, 1, and 6. The bivalent vaccine is approved in the United States for prevention of cervical cancer, cervical intraepithelial neoplasia 2 (CIN 2) or worse, adenocarcinoma in situ (AIS), and CIN 1 caused by HPV types 16 and 18, but not against genital warts. This vaccine is approved for females 9–25 years of age. Meanwhile, the quadrivalent L1 VLP vaccine (HPV types 6, 11, 16, and 18) marketed under the name Gardasil (Merck) is administered intramuscularly at months 0, 2, and 6. The quadrivalent vaccine is approved for (1) vaccination of girls and women ages 9–26 years of age to prevent genital warts and cervical cancer caused by HPV types 6, 11, 16, and 18; (2) vaccination of the same population to prevent precancerous or dysplastic lesions, including cervical AIS, CIN 2/3, vulvar intraepithelial neoplasia 2/3 (VIN 2/3), vaginal intraepithelial neoplasia 2/3 (VaIN 2/3), and CIN 1; (3) vaccination of boys and men 9–26 years of age to prevent genital warts caused by HPV types 6 and 11; and (4) vaccination of people 9–26 years of age to prevent anal cancer and associated precancerous lesions due to HPV types 6, 11, 16, and 18. Also, in 2014, the U.S. Food and Drug Administration approved a new nine-valent L1 VLP vaccine that targets HPV types 6, 11, 16, and 18 (the types also targeted by the quadrivalent HPV vaccine) as well as five additional oncogenic HPV types (31, 33, 45, 52, and 58). The nine-valent vaccine is marketed under the name Gardasil-9 (Merck) and is administered intramuscularly at months 0, 2, and 6. In the United States, the Centers for Disease Control and Prevention now recommends two doses of HPV vaccine (at 0 and 6–12 months) for persons starting the vaccination series before the fifteenth birthday, as the immunologic response is rigorous in this age group. Three doses of HPV vaccine (at 0, 1–2, and 6 months) are recommended for persons starting the vaccination series on or after the fifteenth birthday and for persons with certain immunocompromising conditions, including HIV/AIDS. No therapeutic effect of either vaccine against active infection or disease has been documented. Women who have received HPV vaccination should continue to receive standard Pap smear testing to detect disease caused by other oncogenic HPV types. Because 30% of cervical cancers are caused by HPV types not contained in the vaccines, no changes in cervical cancer screening programs are currently recommended.

III-200. The answer is D. *(Chap. 194)* This patient presents with symptoms of the common cold. Influenza viruses, respiratory syncytial virus (RSV), and human metapneumovirus (hMPV) are the most common causes of serious lower respiratory tract disease in otherwise healthy subjects; parainfluenza viruses (PIVs) and adenoviruses also cause substantial lower respiratory tract disease. Rhinoviruses (the most common cause of the common cold syndrome) have been increasingly associated with lower respiratory tract syndromes. Rhinovirus infection is so common, even in asymptomatic individuals, that it has been hard to establish clear figures for the role of rhinovirus in lower respiratory disease. Infections with most of the conventional respiratory viruses (e.g., influenza virus, RSV, and hMPV) occur in winter. Typically, there is one dominant virus sweeping through a local community at any one time, a pattern that suggests some population-level interference with transmission. Multiplex panels of reverse transcription-polymerase chain reaction tests capable of detecting a dozen or more viruses are commonly available for clinical testing of respiratory secretions. These sensitive tests have been especially helpful in studies of infection in adults, who often shed much lower concentrations of virus in secretions than do children. Rhinoviruses have single-stranded, positive-sense RNA genomes. Rhinoviruses A through C represent species in the *Enterovirus* genus of the family Picornaviridae. Rhinoviruses are the most common viral infective agents in humans and the most frequent cause of the common cold. Most respiratory viruses do not spread by small-particle aerosols across rooms or down halls, although measles virus and varicella-zoster virus do spread in this manner. Therefore, contact and droplet precautions are sufficient to prevent transmission in most settings and airborne precautions are not necessary; handwashing is especially critical in health care settings during the winter.

III-201. The answer is C. *(Chap. 194)* Acute viral respiratory illnesses are the most common illness worldwide, and a wide variety of viruses have been implicated as causes. Rhinoviruses are the most common virus causing the common cold and are found in about 50% of cases.

The second most commonly isolated viruses are coronaviruses. These viruses are more common in the late fall, winter, and early spring, primarily at times when rhinoviruses are less active. Adenoviruses are another cause of common cold in children, although this virus is uncommon in adults with the exception of outbreaks in individuals living in close quarters such as military recruits. Although human respiratory syncytial virus characteristically causes pneumonia and bronchiolitis in young children, the virus can cause common cold and pharyngitis in adults. Parainfluenza virus is another virus classically associated with croup in children, but causes common cold in adults. Enteroviruses most commonly cause an undifferentiated febrile illness.

III-202. The answer is A. *(Chap. 193)* The common viruses causing respiratory infections often have specific associated clinical syndromes. Rhinoviruses are primarily responsible for the common cold. Coronaviruses are also commonly associated with the cold, with the exception of MERS, SARS, and SARS-CoV-2, which may cause severe lower respiratory tract illness and acute respiratory distress syndrome. Human respiratory syncytial virus (HRSV) is the primary agent responsible for lower respiratory disease and bronchiolitis in infants and young children. Another virus primarily associated with childhood illness is parainfluenza virus. This virus is a frequent cause of croup in young children characterized by a febrile illness with a barking cough and stridor. Adenovirus often causes a febrile illness with common cold and pharyngitis in children. In adults, it is associated with outbreaks of respiratory illness in military recruits and in colleges. Herpes simplex virus is associated gingivostomatitis in children and pharyngotonsillitis in adults.

III-203. The answer is D. *(Chap. 194)* This patient has measles. Measles virus probably is the most contagious respiratory virus infection of humans: it is transmitted efficiently not only by direct contact with infected persons or fomites (like other respiratory viruses) but also by small-particle aerosols. Measles virus infection is preventable by vaccination but is so infectious that cases are inevitable—even in the United States—whenever vaccination rates fall below 90–95% in a population. The virus causes systemic illness, sometimes including severe pneumonia, when primary infection occurs in an unvaccinated adult or an immunocompromised person of any age. Therefore, vigilance in maintaining high vaccination rates is critical. With primary infection, the illness in children is typically milder; however, mortality rates in low-resource countries are high, especially among persons with underlying risk factors, including malnutrition. Symptoms of measles include ≥3 days of high fever and a classical set of upper and lower respiratory tract symptoms sometimes termed “the 3 Cs”: cough, coryza, and conjunctivitis. Unlike most respiratory viruses, measles virus circulates in the bloodstream and thus causes disseminated infection with systemic manifestations. Usually, a characteristic diffuse maculopapular rash appears within days of fever onset. Koplik spots—typical mucosal lesions in the mouth that appear briefly—are considered diagnostic of measles infection in the setting of the typical rash and fever. Airborne transmission occurs through the dissemination of airborne droplet nuclei (particles of ≤5 μm) or evaporated droplets containing viruses that can remain suspended in the air for long periods. Certain viruses that are carried by the airborne route can be inhaled by a susceptible host in the same room or over a long distance from the source patient, depending on environmental factors such as temperature and ventilation. Viruses transmitted by this route are SARS-CoV, measles virus, and varicella-zoster virus. Patients with these infections should be managed with personal respiratory protection and special ventilation and air handling. Measles was considered eliminated from the United States in 2000, although outbreaks in 2019 threatened this status.

III-204. **The answer is C.** *(Chap. 196)* This patient has human T-cell lymphotropic virus 1 (HTLV-1)-associated myelopathy (HAM, or tropic spastic paresis), caused by HTLV-1. HAM affects female patients disproportionately. HAM resembles multiple sclerosis in certain ways. The onset is insidious. Symptoms include weakness or stiffness in one or both legs, back pain, and urinary incontinence. Sensory changes are usually mild, but peripheral neuropathy may develop. The disease generally takes the form of slowly progressive and unremitting thoracic myelopathy; one-third of patients are bedridden within 10 years of diagnosis, and one-half are unable to walk unassisted by this point. Patients display spastic paraparesis or paraplegia with hyperreflexia, ankle clonus, and extensor plantar responses. Cognitive function is usually spared; cranial nerve abnormalities are unusual. MRI reveals lesions in both the white matter and the paraventricular regions of the brain as well as in the spinal cord. HTLV-1 infection is transmitted in at least three ways: from mother to child, especially via breast milk; through sexual activity, more commonly from men to women; and through the blood—via contaminated transfusions or contaminated needles. The virus is most commonly transmitted perinatally. HTLV-1 is endemic in southwestern Japan and Okinawa, where >1 million persons are infected. Antibodies to HTLV-1 are present in the serum of up to 35% of Okinawans, 10% of residents of the Japanese island of Kyushu, and <1% of persons in nonendemic regions of Japan. Despite this high prevalence of infection, only ~500 cases of adult T-cell leukemia/lymphoma are diagnosed in this area each year. Clusters of infection have been noted in other areas of eastern Asia, such as Taiwan; in the Caribbean basin, including northeastern South America; in northwestern South America; in central and southern Africa; in Italy, Israel, Iran, and Papua New Guinea; in the Arctic; and in the southeastern part of the United States. Progressive spastic or ataxic myelopathy developing in an individual who is HTLV-1 positive (i.e., who has serum antibodies to HTLV-1) may be due to direct infection of the nervous system with the virus, but destruction of the pyramidal tracts appears to involve HTLV-1-infected CD4+ T cells; a similar disorder may result from infection with HIV or HTLV-2.

III-205. **The answer is C.** *(Chap. 197)* HIV is transmitted primarily by sexual contact (both heterosexual and male to male); by blood and blood products; and by infected mothers to infants intrapartum, perinatally, or via breast milk. After more than 30 years of experience and observations regarding other potential modalities of transmission, there is no evidence that HIV is transmitted by casual contact or that the virus can be spread by insects, such as by a mosquito bite. HIV infection is predominantly a sexually transmitted infection (STI) worldwide. By far, the most common mode of infection, particularly in developing countries, is heterosexual transmission, although in many Western countries a resurgence of male-to-male sexual transmission has occurred (Table III-205). Although a wide variety of factors including viral load and the presence of ulcerative genital diseases influence the efficiency of heterosexual transmission of HIV, such transmission is generally inefficient. A recent systemic review found a low per-act risk of heterosexual transmission in the absence of antiretrovirals: 0.04% for female-to-male transmission and 0.08% for male-to-female transmission during vaginal intercourse in the absence of antiretroviral therapy or condom use. Among various cofactors examined in studies of heterosexual HIV transmission, the presence of other STIs has been strongly associated with HIV transmission. In this regard, there is a close association between genital ulcerations and transmission, because of both susceptibility to infection and infectivity. The quantity of HIV-1 in plasma is a primary determinant of the risk of HIV-1 transmission. In a cohort of heterosexual

TABLE III-205 Estimated Per-Act Probability of Acquiring HIV From an Infected Source, By Exposure Act

Type of Exposure	Risk per 10,000 Exposures
Parenteral	
Blood transfusion	9250
Needle-sharing during injection drug use	63
Percutaneous (needle-stick)	23
Sexual	
Receptive anal intercourse	138
Insertive anal intercourse	11
Receptive penile-vaginal intercourse	8
Insertive penile-vaginal intercourse	4
Receptive oral intercourse	Low
Insertive oral intercourse	Low
Other[a]	
Biting	Negligible
Spitting	Negligible
Throwing body fluids (including semen or saliva)	Negligible
Sharing sex toys	Negligible

[a] HIV transmission through these exposure routes is technically possible but unlikely and not well documented.

Source: Reproduced with permission from Centers for Disease Control and Prevention. Available from www.cdc.gov/hiv/risk/estimates/riskbehaviors.html. Accessed December 14, 2020.

couples in Uganda discordant for HIV infection and not receiving antiretroviral therapy, the mean serum HIV RNA level was significantly higher among HIV-infected subjects whose partners seroconverted than among those whose partners did not seroconvert. In fact, transmission was rare when the infected partner had a plasma level of <1700 copies of HIV RNA per milliliter, even when genital ulcer disease was present.

III-206. The answer is E. *(Chap. 197)* Dermatologic problems occur in >90% of patients with HIV infection. From the macular, roseola-like rash seen with the acute seroconversion syndrome to extensive end-stage Kaposi sarcoma, cutaneous manifestations of HIV disease can be seen throughout the course of HIV infection. Among the more common nonneoplastic problems are seborrheic dermatitis, folliculitis, and opportunistic infections. Extrapulmonary pneumocystosis may cause a necrotizing vasculitis. Dermatologic problems occur in >90% of patients with HIV infection. Kaposi sarcoma is due to coinfection with human herpesvirus-8 in patients with HIV/AIDS. It typically presents as more than one red-purple nodular painless lesion anywhere on the body. Seborrheic dermatitis occurs in 3% of the general population and in up to 50% of patients with HIV infection. Seborrheic dermatitis increases in prevalence and severity as the CD4+ T-cell count declines. In HIV-infected patients, seborrheic dermatitis may be aggravated by concomitant infection with *Pityrosporum*, a yeastlike fungus; use of topical antifungal agents has been recommended in cases refractory to standard topical treatment. Herpes zoster reactivation is painful and dermatomal, with progression of papules to vesicles to small pustules and then crusting. Molluscum contagiosum typically appears as one or many small pearly umbilicated asymptomatic papules occurring anywhere on the body. They can be a significant cosmetic issue in patients with AIDS. Psoriasis is not more common in patients with HIV infection but may be more severe and generalized. It would be uncommon to involve the face only.

III-207. The answer is C. *(Chap. 197)* The quoted risk for HIV transmission via a needlestick is 0.3%. This risk can be reduced to <0.1% if the at-risk health care worker is treated with antiretroviral therapy within 24 hours. The risk of transmission is likely highly variable according to a number of factors. Large-bore needlesticks where infected patient blood is visible are higher risk, as are deep tissue punctures to the health care provider. The patient's degree of virologic control is generally inferred to be critical as well. Patients with a viral load <1500/mL are considerably less likely to transmit the virus via a needlestick than those with high viral loads. An extension of this point is that during acute and end-stage HIV infection, viral loads are extremely high and contagion by needlestick is likely to be much higher. In addition, during end-stage disease, virulent viral forms predominate, which may increase the risk to an even greater extent. Each of these variables must be assessed rapidly after an accidental high-risk needlestick. Antiretroviral therapy (ART) is effective at preventing HIV transmission via needlestick if given before viral RNA incorporates into the host genome as proviral DNA. This is thought to occur within approximately 48 hours, but under the best scenario, ART should be given within an hour of a needlestick. Circumstances are often murky, with key information such as viral load, viral resistance history, and even HIV serostatus of the patient variably available; therefore, urgent consultation with an HIV and/or occupational health specialist is imperative after a needlestick. (Hepatitis B and C transmission must also be considered.)

III-208. The answer is B. *(Chap. 197)* Understanding toxicities of antiretroviral agents is important. Dolutegravir is very well tolerated; while transaminitis has been reported in patients co-infected with hepatitis B or hepatitis C, few other toxicities are common. Fanconi anemia is a rare disorder associated with tenofovir. Abacavir has been associated with fatal hypersensitivity reactions with rechallenge. This hypersensitivity is strongly associated with the HLA-B5701 haplotype, and a hypersensitivity reaction to abacavir is an absolute contraindication to future therapy. Symptoms, which usually occur within 2 weeks of therapy but can take >6 weeks to emerge, include fever, maculopapular rash, fatigue, malaise, gastrointestinal symptoms, and/or dyspnea. Once a diagnosis is suspected, the drug should be stopped and never given again because rechallenge can be fatal. For this reason, both the diagnosis and patient education once the diagnosis is made must be performed thoroughly and carefully. Zidovudine causes macrocytic anemia and sometimes granulocytopenia. Stavudine and other nucleoside reverse transcriptase inhibitors are associated with lipoatrophy of the face and legs.

III-209. The answer is B. *(Chap. 197)* Cytomegalovirus (CMV) colitis should be considered in AIDS patients with CD4+ lymphocyte count <50/μL, fevers, and diarrhea. Diarrhea is often bloody but can be watery. Initial evaluation often involves stool studies to rule out other parasitic or bacterial causes of diarrhea in AIDS patients. A standard panel will include some or all of the following depending on epidemiologic and historical data: *Clostridium difficile* stool antigen, stool culture, stool *Mycobacterium avium* intracellulare culture, stool ova and parasite examination, and special stains for *Cryptosporidium*, *Isospora*, *Cyclospora*, and *Microsporidium*. There is no stool or serum test that is useful for the evaluation of CMV colitis in an HIV-infected patient. A positive CMV IgG is merely a marker of past infection. If this test is negative, then the pretest probability of developing active CMV decreases substantially. Serum CMV polymerase chain reaction (PCR) has gained utility in solid organ and bone marrow transplant patients for following treatment response for invasive CMV infection. However, in HIV-infected patients, CMV viremia correlates imprecisely with colitis. Further, because CMV is a latent-lytic herpesvirus, a positive serum PCR does not imply disease unless drawn in the right clinical context, for which there is none in HIV infection. Colonic histology is sensitive and specific for the diagnosis of CMV colitis, with large-cell inclusion bodies being diagnostic.

III-210. The answer is B. *(Chap. 197)* Immune reconstitution syndrome (IRIS) is commonly seen after the initiation of antiretroviral treatment (ART) in patients with AIDS and a concomitant opportunistic infection (OI). It is a syndrome where either a previously recognized OI (such as *Mycobacterium avium*) worsens after ART despite an initial period of improvement after standard therapy for that particular infection, or when an OI that was not previously recognized is unmasked after ART therapy. The latter scenario occurs presumably as immune cells become reactivated and recognize the presence of a pathogen that disseminated in the absence of adequate T-cell response with the patient remaining subclinical prior to ART. Many opportunistic pathogens are known to behave this way, but *Cryptococcus*, *M. tuberculosis*, and *M. avium* intracellulare/*M. avium* complex (MAI/MAC) are the most likely to be associated with IRIS. Risk factors for IRIS are CD4+

lymphocyte count <50/μL at ART initiation, initiation of ART within 2 months of treatment initiation for the OI, adequate virologic response to ART, and increase in CD4+ lymphocyte count as a result of ART. IRIS can be diagnostically challenging and is very diverse in terms of clinical presentation and severity. Depending on the organ system and pathogen involved, drug-resistant OI and new OI must be considered, sometimes necessitating invasive biopsies and cultures. In this case, the overlap of the organ systems with the original presentation, low likelihood of MAI drug resistance, and timing of the syndrome favor IRIS. Therapy is with nonsteroidal anti-inflammatory drugs and sometimes glucocorticoids. OI treatment is continued, as is HIV ART therapy.

III-211. **The answer is B.** *(Chap. 197)* The Centers for Disease Control and Prevention guidelines now state that all adults should receive HIV testing, with the availability of a patient opt-out mechanism rather than informed consent. The basis for this is that approximately 25% of the 1 million Americans infected with HIV are unaware of their status, there is good available treatment for HIV that serves to extend the life span and decrease HIV transmission, and HIV testing is shown to correlate with a decrease in risk-taking behaviors. Cost-benefit analysis has suggested this approach has advantages compared with current approaches focusing on screening high-risk populations. Pretest counseling is desirable but not always built into the testing process, so physicians should provide some degree of preparation for a positive test. If the diagnosis is made, support systems should be activated that may include trained nurses, social workers, or community support centers.

III-212. **The answer is A.** *(Chap. 197)* This patient most likely has HIV encephalopathy of moderate severity. Other neurologic conditions associated with HIV may be considered with a broad initial workup, but her reasonably high CD4+ count, lack of focal deficits, and lack of mass lesions on high-resolution brain imaging make toxoplasmosis, central nervous system (CNS) tuberculoma, progressive multifocal leukoencephalopathy (PML), or CNS lymphoma all less unlikely. Immediate highly active antiretroviral therapy is the treatment of choice for HIV encephalopathy, and this patient warrants this treatment despite her CD4+ lymphocyte count placing her in a gray zone according to current guidelines in regard to starting therapy. A lumbar puncture for VDRL is unnecessary as a serum rapid plasmin reagin test is a very good screening test for any type of syphilis; JC virus detected in the CSF would suggest PML, but her pretest probability for this is low because it usually affects patients with a low CD4+ T-cell count. Serum cryptococcal antigen has excellent performance characteristics, but there is little reason to suspect cryptococcal meningitis in the absence of headache or elevated intracerebral pressure.

III-213. **The answer is B.** *(Chap. 197)* Cryptosporidia, microsporidia, and *Isospora belli* are the most common opportunistic protozoa that infect the gastrointestinal tract and cause diarrhea in HIV-infected patients. Cryptosporidial infection may present in a variety of ways, ranging from a self-limited or intermittent diarrheal illness in patients in the early stages of HIV infection to a severe, life-threatening diarrhea in severely immunodeficient individuals. In patients with untreated HIV infection and CD4+ T-cell counts of <300/μL, the incidence of cryptosporidiosis is ~1% per year. In 75% of cases the diarrhea is accompanied by crampy abdominal pain, and 25% of patients have nausea and/or vomiting. Cryptosporidia may also cause biliary tract disease in the HIV-infected patient, leading to cholecystitis with or without accompanying cholangitis and pancreatitis secondary to papillary stenosis. The diagnosis of cryptosporidial diarrhea is made by stool examination or biopsy of the small intestine. The diarrhea is noninflammatory, and the characteristic finding is the presence of oocysts that stain with acid-fast dyes. Therapy is predominantly supportive, and marked improvements have been reported in the setting of effective combination antiretroviral therapy. Treatment with up to 2000 mg/d of nitazoxanide is associated with improvement in symptoms or a decrease in shedding of organisms in about half of patients. Its overall role in the management of this condition remains unclear. Patients can minimize their risk of developing cryptosporidiosis by avoiding contact with human and animal feces, by not drinking untreated water from lakes or rivers, and by not eating raw shellfish.

III-214. The answer is D. *(Chap. 197)* Acute HIV should be suspected in any at-risk person who presents with a mono-like illness; it is diagnosed by positive plasma RNA polymerase chain reaction (PCR). Patients typically have not developed sufficient antibodies to the virus yet to develop a positive enzyme immunoassay, and the diagnosis of HIV is usually missed if this test is sent within the first 2 months of HIV acquisition. It is tempting for clinicians to send an ultrasensitive PCR, but this only decreases specificity (false-positive tests with detection of very low levels of HIV are possible due to cross-contamination in the laboratory) with no other benefit. There is typically a massive amount of HIV virus in the plasma during acute infection, and the ultrasensitive assay is never required for detection at this stage of disease. Ultrasensitive assays are helpful in the context of therapy to ensure that there is no persistence of low-level viremia. CD4+ lymphocyte count decreases during many acute infections, including HIV, and is therefore not diagnostically appropriate. CD4+ lymphocyte counts are useful to risk stratify for opportunistic infection in stable patients with known HIV infection. Resistance tests are sent only when the diagnosis is confirmed.

III-215. The answer is D *(Chap. 197)* Oral lesions, including *thrush*, *hairy leukoplakia*, and *aphthous ulcers*, are particularly common in patients with untreated HIV infection (Figure III-215B). Thrush, due to *Candida* infection, and oral hairy leukoplakia, presumed due to Epstein-Barr virus (EBV), are usually indicative of fairly advanced immunologic

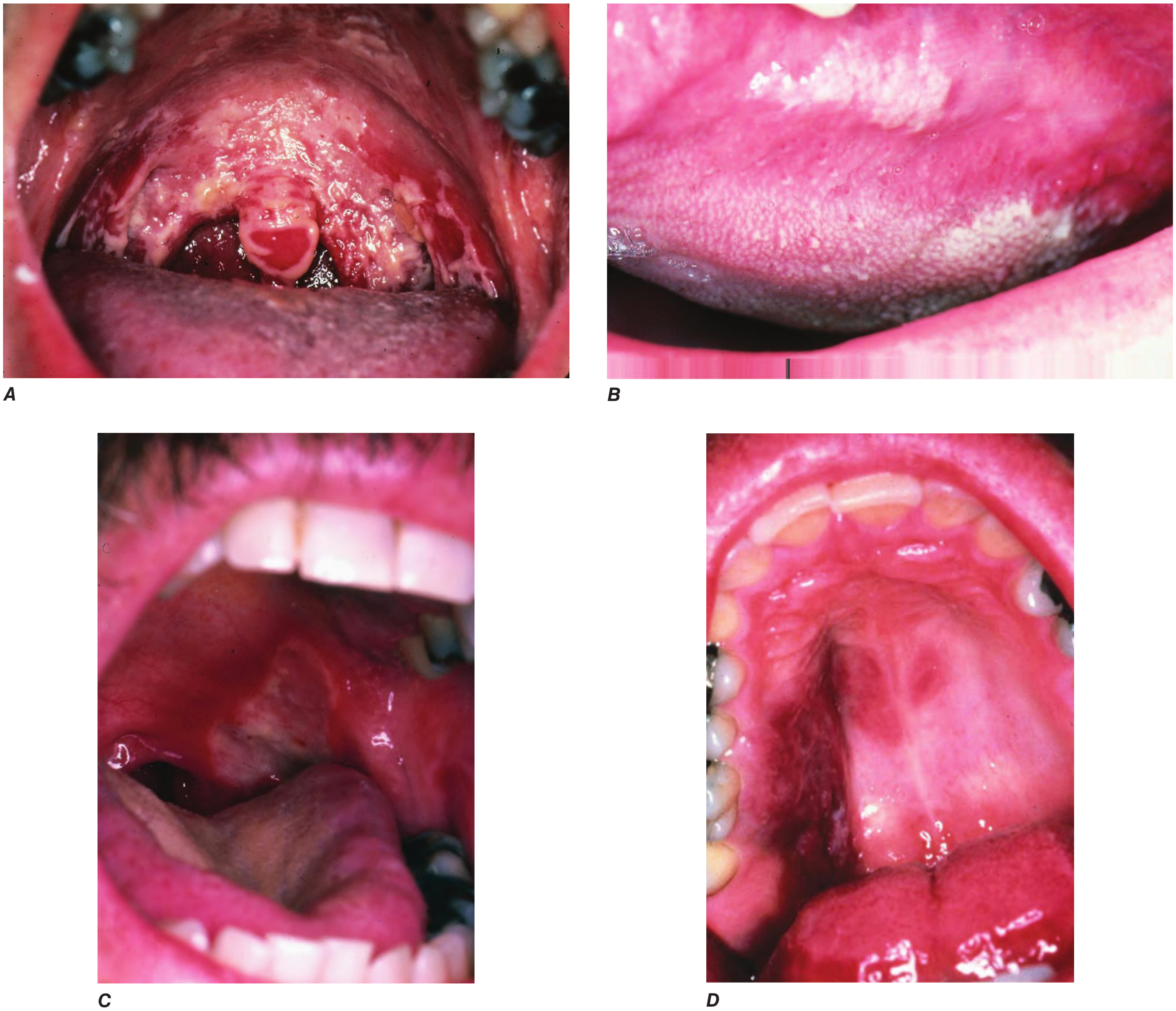


FIGURE III-215B Various oral lesions in HIV-infected individuals. ***(A)*** Thrush. ***(B)*** Hairy leukoplakia. ***(C)*** Aphthous ulcer. ***(D)*** Kaposi sarcoma.

decline; they generally occur in patients with CD4+ T-cell counts of <300/μL. In one study, 59% of patients with oral candidiasis went on to develop AIDS in the next year. Thrush appears as a white, cheesy exudate, often on an erythematous mucosa in the posterior oropharynx. While most commonly seen on the soft palate, early lesions are often found along the gingival border. The diagnosis is made by direct examination of a scraping for pseudohyphal elements. Culturing is of no diagnostic value, as patients with HIV infection may have a positive throat culture for *Candida* in the absence of thrush. Oral hairy leukoplakia presents as white, frondlike lesions, generally along the lateral borders of the tongue and sometimes on the adjacent buccal mucosa. Despite its name, oral hairy leukoplakia is not considered a premalignant condition. Lesions are associated with florid replication of EBV. While usually more disconcerting as a sign of HIV-associated immunodeficiency than a clinical problem in need of treatment, severe cases have been reported to respond to topical podophyllin or systemic therapy with anti-herpesvirus agents. Aphthous ulcers of the posterior oropharynx also are seen with regularity in patients with untreated HIV infection. These lesions are of unknown etiology and can be quite painful and interfere with swallowing. Topical anesthetics provide immediate symptomatic relief of short duration. The fact that thalidomide is an effective treatment for this condition suggests that the pathogenesis may involve the action of tissue-destructive cytokines. Palatal, glossal, or gingival ulcers may also result from cryptococcal disease or histoplasmosis.

III-216. The answer is D. (*Chap. 197,* https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf). Pre-exposure prophylaxis (PrEP) using oral antiretroviral drugs such as Truvada (tenofovir disoproxil fumarate [TDF] + emtricitabine [FTC]) as a single daily pill is highly efficacious in preventing acquisition of HIV infection. The degree of efficacy can be greater than 95% if subjects adhere strictly to the regimen. The Centers for Disease Control and Prevention estimates that approximately 1.2 million people in the United States are at "substantial risk" for HIV infection and should be counseled about PrEP. As of 2016, however, fewer than half of primary physicians and nurses have heard of PrEP. Daily oral PrEP with the fixed-dose combination of TDF 300 mg and FTC 200 mg has been shown to be safe and effective in reducing the risk of sexual HIV acquisition in adults; therefore, PrEP is recommended as one prevention option for sexually active adult men who have sex with men at substantial risk of HIV acquisition, for adult heterosexually active men and women who are at substantial risk of HIV acquisition, and for adult persons who inject drugs (also called injection drug users) at substantial risk of HIV acquisition. PrEP should be discussed with heterosexually active women and men whose partners are known to have HIV infection (i.e., HIV-discordant couples) as one of several options to protect the uninfected partner during conception and pregnancy so that an informed decision can be made in awareness of what is known and unknown about benefits and risks of PrEP for mother and fetus. Health care workers in an HIV clinic should not be at occupational high risk of acquiring HIV infection.

III-217. The answer is B. (*Chap. 197,* https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/11/what-to-start--initial-combination-regimens-for-the-antiretroviral-naive-patient) Therapy of HIV infection does not lead to eradication or cure of HIV. Treatment decisions must take into account that one is dealing with a chronic infection. Patients initiating antiretroviral therapy (ART) must be willing to commit to lifelong treatment and understand the importance of adherence to their prescribed regimen. Treatment interruption regimens are associated with rapid increases in HIV RNA levels, rapid declines in CD4+ T-cell counts, and an increased risk of clinical progression. In clinical trials, there has been an increase in serious adverse events in the patients randomized to intermittent therapy, suggesting that some "non–AIDS-associated" serious adverse events such as heart attack and stroke may be linked to HIV replication. Given that patients can be infected with viruses that harbor drug-resistance mutations, it is recommended that a viral genotype be done prior to the initiation of therapy to optimize the selection of antiretroviral agents. The options currently recommended are bictegravir/tenofovir, alafenamide/emtricitabine, dolutegravir/abacavir/lamivudine, dolutegravir plus (emtricitabine or lamivudine) plus (tenofovir alafenamide [TAF] or tenofovir disoproxil fumarate

[TDF]), dolutegravir/lamivudine, and raltegravir plus (emtricitabine or lamivudine) plus (TAF or TDF). Following the initiation of therapy, one should expect a rapid, at least 1-log (10-fold) reduction in plasma HIV RNA levels within 1–2 months and then a slower decline in plasma HIV RNA levels to <50 copies per milliliter within 6 months. There should also be a rise in the CD4+ T-cell count of 100–150/μL that is also particularly brisk during the first month of therapy. Subsequently, one should anticipate a CD4+ T-cell count increase of 50–100 cells/year until numbers approach normal. Many clinicians feel that failure to achieve these end points is an indication for a change in therapy.

III-218. The answer is D. *(Chap. 198) Norovirus* is a member of the Caliciviridae family and is a common cause of diarrhea. It is thought that noroviruses are the most common infectious agents causing mild gastroenteritis in the community. These viruses also commonly cause traveler's diarrhea and can occur in large outbreaks when individuals are confined in close quarters such as on cruise ships or in the military. It affects all age groups and is transmitted by the fecal-oral route. The virus is also present in vomitus. Inoculum with only a very few viral particles can be infectious, and the estimated case rate after exposure is 50%. Clinically, patients typically present with a sudden onset of nausea, vomiting, diarrhea, and crampy abdominal pain within 24 hours of exposure. The illness can last from 12 to 60 hours, and systemic symptoms including fever, chills, headache, and myalgias may occur. The stools are loose and watery without blood. Abdominal examination is generally benign. Death only rarely occurs and typically only in vulnerable individuals who have chronic health conditions exacerbated by dehydration. After acquiring norovirus, immunity is only short-lived, and an individual may become reinfected with a new exposure. Diagnosis is typically made on clinical grounds, although public health officials will frequently use enzyme immunoassays for assessing an acute outbreak such as the one described. Treatment is supportive only as the disease is self-limited. Rotaviruses are the leading cause of diarrheal death in children in the developing world, but generally only cause mild gastroenteritis in adults. With the introduction of the rotavirus vaccine, cases and hospitalizations due to rotavirus have declined. Rotavirus does not typically cause outbreaks of traveler's diarrhea. *Bacillus cereus* and *Staphylococcus aureus* are both causes of food poisoning that should be included in the differential diagnosis. However, the large outbreak of illness makes norovirus more likely. Enterotoxigenic *Escherichia coli* is a frequent cause of traveler's diarrhea to tropical areas due to ingestion of contaminated foods or water. Affected patients would have been unlikely to have all been exposed during disembarkment, and the large outbreak is also not consistent with this diagnosis.

III-219. The answer is A. *(Chap. 200)* The oral mucosal lesion is a Koplik spot, characteristic of measles infection. Measles remains a common illness worldwide and continues to pose a significant health threat in the United States among individuals who are unvaccinated. Prior to the availability of the measles vaccine, an estimated 3–5 million individuals died of measles and its complications yearly. However, since the introduction of the measles vaccine in the 1960s, the number of cases of measles worldwide has declined. By 2008, the estimated number of deaths due to measles had declined to <200,000 yearly, but measles remains a common cause of death among children under the age of 5 in developing countries. Areas that continue to have a high number of measles cases include India, Pakistan, China, and Southeast Asia. Some areas of Africa also have greater numbers of measles cases. Measles is caused by a single-stranded RNA virus that is a member of the *Morbillivirus* genus. It is one of the most highly contagious directly transmitted pathogens. Outbreaks can occur in populations even if <10% of the individuals are susceptible. Susceptible household contacts have attack rates of >90%. Frequent settings for outbreaks include schools and health care settings. The virus is transmitted by respiratory droplets in short distances or, less commonly, by small-particle aerosols that remain suspended in the air for long periods. After exposure, there is a 10-day incubation period. During this time, the virus is replicating locally in the respiratory epithelium with development of a secondary viremia at 5–7 days. Prior to symptom onset and during viral replication, affected individuals can shed high numbers of viral particles, fostering further spread of disease. After the incubation period, initial symptoms include fever, malaise, cough, conjunctivitis, and coryza. Koplik spots are diagnostic of measles. The bluish white dots appear initially on the buccal mucosa and are surrounded by erythema. They precede the onset of rash typically by 2 days. The rash of measles is erythematous and macular. It begins most commonly behind the ears and along the neck and hairline. It progresses to involve the face, trunk, and arms, where it may become confluent. Petechiae may be present. The rash fades in the same order of progression, and desquamation of the skin may occur. Deaths due to measles occur related to respiratory complications including bacterial pneumonia as well as encephalitis. In developed countries, the case-fatality rate of measles in children is <1 in 1000, but death rates as high as 20–30% can occur in refugee camps. Vaccination is highly effective in measles prevention. Infants who have been vaccinated develop effective immunity by the age of 9 months in 85% of cases and by the age of 12 months in 95% of cases. Rates of secondary vaccine failure are low, typically around 5% or less, even 10–15 years after vaccination. Due to the misconception that measles vaccination is associated with the development of autism, there has been an anti-vaccination movement in the United States, with periodic outbreaks as a result. In this setting, the disease is most often introduced by an affected individual who recently traveled to an area where measles remains common.

III-220. The answer is E. *(Chap. 200)* There is no specific antiviral therapy for measles. Treatment should include supportive measures such as hydration and management of fever. Vitamin A is effective for the treatment of measles and can reduce morbidity and mortality rates. The World Health Organization recommends administering vitamin A 200,000 units orally once per day for 2 consecutive days. A third dose is recommended 2–4 weeks later if there is documented vitamin A deficiency. If a secondary bacterial infection is suspected based on clinical findings such as pneumonia or otitis media, then antibiotics should be initiated at that time. There is no evidence to support prophylactic use of antibiotics.

III-221. The answer is D. *(Chap. 201)* This patient has rubella, or German measles. Acquired rubella commonly presents with a generalized maculopapular rash that usually lasts for up to 3 days, although as many as 50% of cases may be subclinical or without rash. When it occurs, the rash is usually mild and may be difficult to detect in persons with darker skin. In children, rash is usually the first sign of illness. However, in older children and adults, a 1- to 5-day prodrome often precedes the rash and may include low-grade fever, malaise, and upper respiratory symptoms. The incubation period is 14 days (range, 12–23 days). Lymphadenopathy, particularly occipital and postauricular, may be noted during the second week after exposure. Although acquired rubella is usually thought of as a benign disease, arthralgia and arthritis are common in infected adults, particularly women. Thrombocytopenia and encephalitis are less common complications. The most serious consequence of rubella virus infection can develop when a woman becomes infected during pregnancy, particularly during the first trimester, as in this case (Table III-221). The resulting complications may include miscarriage, fetal death, premature delivery, or live birth with congenital defects. Infants infected with rubella virus in utero may have myriad physical defects, which most commonly relate to the eyes, ears, and heart. This

TABLE III-221 Common Transient and Permanent Manifestations in Infants with Congenital Rubella Syndrome

Transient Manifestations	Permanent Manifestations
Hepatosplenomegaly	Hearing impairment/deafness
Interstitial pneumonitis	Congenital heart defects (patent ductus arteriosus, pulmonary arterial stenosis)
Thrombocytopenia with purpura/petechiae (e.g., dermal erythropoiesis or "blueberry muffin syndrome")	Eye defects (cataracts, cloudy cornea, microphthalmos, pigmentary retinopathy, congenital glaucoma)
Hemolytic anemia	Microcephaly
Bony radiolucencies	Central nervous system sequelae (mental and motor delay, autism)
Intrauterine growth retardation	
Adenopathy	
Meningoencephalitis	

constellation of severe birth defects is known as congenital rubella syndrome (CRS). In addition to permanent manifestations, there are a host of transient physical manifestations, including thrombocytopenia with purpura/petechiae (e.g., dermal erythropoiesis, "blueberry muffin syndrome"). Abnormal notched or peg-shaped teeth ("Hutchinson teeth") are associated with congenital syphilis. No specific therapy is available for rubella virus infection. Symptom-based treatment for various manifestations, such as fever and arthralgia, is appropriate. Ig does not prevent rubella virus infection after exposure and therefore is not recommended as routine postexposure prophylaxis. Although Ig may modify or suppress symptoms, it can create an unwarranted sense of security: infants with congenital rubella have been born to women who received Ig shortly after exposure. Administration of Ig should be considered only if a pregnant woman who has been exposed to a person with rubella will not consider termination of the pregnancy under any circumstances. In such cases, IM administration of 20 mL of Ig within 72 hours of rubella exposure may reduce—but does not eliminate—the risk of rubella. The most effective method of preventing acquired rubella and CRS is through vaccination with a rubella-containing vaccine. One dose induces seroconversion in ≥95% of persons ≥1 year of age. Immunity is considered long-term and is probably lifelong.

III-222. **The answer is D.** *(Chap. 202)* This patient presents with mumps. Mumps is an illness characterized by acute-onset unilateral or bilateral tender, self-limited swelling of the parotid or other salivary gland(s) that lasts at least 2 days and has no other apparent cause. During a mumps outbreak, the diagnosis is made easily in patients with parotitis and a history of recent exposure. Up to half of mumps virus infections are asymptomatic or lead to nonspecific respiratory symptoms. The prodrome of mumps consists of low-grade fever, malaise, myalgia, headache, and anorexia. Mumps parotitis or swelling of other salivary glands usually occurs within 24 hours of prodromal symptoms but sometimes as long as 1 week thereafter. Parotitis is generally bilateral, although the two sides may not be involved synchronously. Unilateral involvement occurs in about one-third of cases. Swelling of the parotid is accompanied by tenderness and obliteration of the space between the earlobe and the angle of the mandible. The patient frequently reports an earache and finds it difficult to eat, swallow, or talk. The orifice of the parotid duct is commonly red and swollen. The submaxillary and sublingual glands are involved less often than the parotid gland and are almost never involved alone. Glandular swelling increases for a few days and then gradually subsides, disappearing within 1 week. Recurrent sialadenitis is a rare sequela of mumps parotitis. In ~6% of mumps cases, obstruction of lymphatic drainage secondary to bilateral salivary-gland swelling may lead to presternal pitting edema. Epididymo-orchitis, as in this case, is the next most common manifestation of mumps, developing in 15–30% of cases in postpubertal males, with bilateral involvement in 10–30% of those cases. Orchitis, accompanied by fever, typically occurs during the first week of parotitis but can develop up to 6 weeks after parotitis or in its absence. The testis is painful and tender and can be enlarged to several times its normal size; this condition usually resolves within 1 week. Testicular atrophy develops in one-half of affected men. Sterility after mumps is rare, although subfertility is estimated to occur in 13% of cases of unilateral orchitis and in 30–87% of cases of bilateral orchitis. Immunity to mumps is associated with the development of neutralizing antibodies, although a specific correlate of protection has not been established. Seroconversion occurs in ~95% of recipients of the Jeryl Lynn strain; however, the vaccine efficacy rate is ~78% for one dose and 88% for two doses. In several studies, seropositivity rates and vaccine efficacy have declined with time since vaccination.

III-223. **The answer is D.** *(Chap. 203)* The patient has been bitten by a member of a species known to carry rabies in an area in which rabies is endemic. Based on the animal vector and the facts that the skin was broken and that saliva possibly containing the rabies virus was present, postexposure rabies prophylaxis should be administered. If an animal involved in an unprovoked bite can be captured, it should be killed humanely and the head should be sent immediately to an appropriate laboratory for rabies examination by the technique of fluorescent antibody staining for viral antigen. If a healthy dog or cat bites a person in an endemic area, the animal should be captured, confined, and observed for 10 days. If the animal remains healthy for this period, the bite is highly unlikely to have transmitted rabies. Postexposure prophylactic therapy includes vigorous cleaning of the wound with a 20% soap solution to remove any virus particles that may be present. Tetanus toxoid and antibiotics should also be administered. Passive immunization with anti-rabies antiserum in the form of human rabies Ig (rather than the corresponding equine antiserum because of the risk of serum sickness) is indicated at a dose of 10 units/kg into the wound and 10 units/kg IM into the gluteal region. Second, one should actively immunize with an anti-rabies vaccine (either human diploid cell vaccine or rabies vaccine absorbed) in five 1-mL doses given IM, preferably in the deltoid or anterior lateral thigh area. The five doses are given over a 28-day period. The administration of either passive or active immunization without the other modality results in a higher failure rate than does the combination therapy.

III-224. The answer is B. *(Chap. 204)* This patient has a typical presentation of dengue fever. Dengue is probably the most important arthropod-borne viral disease worldwide, with ~390 million infections occurring per year, of which ~96 million cause signs of disease. Year-round transmission of dengue viruses 1–4 occurs between latitudes 25°N and 25°S, but seasonal forays of the viruses into the United States and Europe have been documented. All four viruses have *Aedes aegypti* mosquitoes as their principal vectors. Through increasing spread of mosquitoes throughout the tropics and subtropics and international travel of infected humans, large areas of the world have become vulnerable to the introduction of dengue viruses. Thus, dengue and severe dengue are becoming increasingly common. For instance, conditions favorable to dengue virus 1–4 transmission via *A. aegypti* mosquitoes exist in Hawaii and the southern United States. Dengue begins after an incubation period averaging 4–7 days, when the typical patient experiences the sudden onset of fever, frontal headache, retro-orbital pain, and back pain along with severe myalgias. These symptoms gave rise to the colloquial designation of dengue as "break-bone fever." Often a transient macular rash appears on the first day, as do adenopathy, palatal vesicles, and scleral injection. The illness may last a week, with additional symptoms and clinical signs usually including anorexia, nausea or vomiting, and marked cutaneous hypersensitivity. Near the time of defervescence on days 3–5, a maculopapular rash begins on the trunk and spreads to the extremities and the face. Epistaxis and scattered petechiae are often noted in uncomplicated dengue, and pre-existing gastrointestinal lesions may bleed during the acute illness. Laboratory findings of dengue include leukopenia, thrombocytopenia, and, in many cases, elevations of serum aminotransferase concentrations. The diagnosis is made by IgM enzyme-linked immunosorbent assay (ELISA) or paired serology during recovery or by antigen-detection ELISA or reverse transcriptase-polymerase chain reaction during the acute phase. Several weeks after convalescence from infection with dengue virus 1, 2, 3, or 4, the transient protection conferred by that infection against reinfection with a heterotypic dengue virus usually wanes. Heterotypic reinfection may result in classic dengue or, less commonly, in severe dengue. Among the millions of dengue virus 1–4 infections, ~500,000 cases of severe dengue occur annually, with a lethality of ~2.5%.

III-225. The answer is D. *(Chap. 204)* Disease caused by chikungunya virus is endemic in rural areas of Africa. Intermittent epidemics take place in towns and cities of both Africa and Asia. *Aedes aegypti* mosquitoes are the usual vectors for the disease in urban areas. In 2004, a massive epidemic began in the Indian Ocean region (in particular on the islands of Réunion and Mauritius) and was most likely spread by travelers. The Asian tiger mosquito (*A. albopictus*) was identified as the major vector of chikungunya virus during that epidemic. From 2013 and 2014, several thousand chikungunya virus infections were reported (and several tens to hundreds of thousands of cases were suspected) from Caribbean islands. The virus was imported to Italy, France, and the United States by travelers from the Caribbean. Chikungunya virus poses a threat to the continental United States as suitable vector mosquitoes are present in southern states. The disease is most common among adults, in whom the clinical presentation may be dramatic. The abrupt onset of chikungunya virus disease follows an incubation period of 2–10 days. Fever (often severe) with a saddleback pattern and severe arthralgia are accompanied by chills and constitutional symptoms and signs, such as abdominal pain, anorexia, conjunctival injection, headache, nausea, and photophobia. Migratory polyarthritis mainly affects the small joints of the ankles, feet, hands, and wrists, but the larger joints are not necessarily spared. Rash may appear at the outset or several days into the illness; its development often coincides with defervescence, which occurs around day 2 or 3 of the disease. The rash is most intense on the trunk and limbs and may desquamate. Young children develop less prominent signs and are therefore less frequently hospitalized. Children also often develop a bullous rather than a maculopapular/petechial rash. Maternal–fetal transmission has been reported and, in some cases, has led to fetal death. Recovery may require weeks, and some elderly patients may continue to experience joint pain, recurrent effusions, or stiffness for several years. This persistence of signs and symptoms may be especially common in human leukocyte antigen B27 subtype–positive patients. In addition to arthritis, petechiae are occasionally seen. A few patients develop leukopenia. Elevated concentrations of aspartate aminotransferase and C-reactive protein have been described, as have mildly decreased platelet counts. Treatment of chikungunya virus disease relies on nonsteroidal anti-inflammatory drugs and sometimes chloroquine for refractory arthritis, but there are no specific antiviral treatments.

III-226. The answer is D. *(Chap. 204)* Zika virus is not a viral hemorrhagic fever. Infections with Zika virus are usually asymptomatic or benign and self-resolving, and are most likely misdiagnosed as dengue or influenza. Zika virus disease is typically characterized by low-grade fever, headache, and malaise. An itchy maculopapular rash, nonpurulent conjunctivitis, myalgia, and arthralgia usually accompany or follow those manifestations. Vomiting, hematospermia, and hearing impairments are relatively common clinical signs. In severe cases, Zika virus infection is associated with serious complications such as Guillain-Barré syndrome or fetal microcephaly after congenital transmission. Other neurologic complications of Zika virus infection are encephalitis, meningoencephalitis, transverse myelitis, peripheral neuropathies, retinopathies, and neurologic birth defects. Unfortunately, antiviral treatments (curative or preventive) and licensed vaccines against Zika virus are not yet available.

III-227. The answer is B. (*Chap. 205,* https://www.cdc.gov/vhf/ebola/prevention/index.html) Several viruses of the family Filoviridae cause severe and frequently fatal viral hemorrhagic fevers in humans, including Ebola virus. Introduction of filoviruses into human populations is an extremely rare event that most likely occurs by direct or indirect contact with healthy mammalian filovirus hosts or by contact with infected, sick, or deceased nonhuman primates. Filoviruses are highly infectious but not very contagious. Natural human-to-human transmission takes place through direct person-to-person (usually skin-to-skin) contact or exposure to infected bodily fluids and tissues; there is no evidence of such transmission by aerosol or respiratory droplets. The first phase (disease onset until around day 5–7) resembles influenza and is characterized by sudden onset of fever and chills, severe headaches, cough, myalgia, pharyngitis, arthralgia of the larger joints, development of a maculopapular rash, and other systemic signs/symptoms. The second phase (approximately 5–7 days after disease onset and thereafter) typically involves the gastrointestinal tract (abdominal pain with vomiting and/or diarrhea) respiratory tract (chest pain, cough), vascular system (postural hypotension, edema), and central nervous system (confusion, coma, headache). Hemorrhagic manifestations such as subconjunctival injection, nosebleeds, hematemesis, hematuria, and melena are also typical. Common laboratory findings are leukopenia (with cell counts as low as 1000/μL) with a left shift prior to leukocytosis, thrombocytopenia (with counts as low as 50,000/μL), increased concentrations of liver and pancreatic enzymes hypokalemia, hypoproteinemia, increased creatinine and urea concentrations with proteinuria, and prolonged prothrombin and partial thromboplastin times. Patients usually succumb to disease 4–14 days after infection. Patients who survive experience prolonged and sometimes incapacitating sequelae such as arthralgia, asthenia, iridocyclitis, hearing loss, myalgia, orchitis, parotitis, psychosis, recurrent hepatitis, transverse myelitis, or uveitis. Temporary hair loss and desquamation of skin areas previously affected by a typical maculopapular rash are visible consequences of the disease. Rarely, filoviruses can persist in the liver, eyes, or testicles of survivors and may cause recurrent disease months after convalescence. Any treatment of patients with suspected or confirmed filovirus infection must be administered under increased safety precautions by experienced specialists using appropriate personal protective equipment. Treatment of EVD is entirely supportive because no accepted/approved, efficacious, specific antiviral agents are yet available. On December 19, 2019, the U.S. Food and Drug

Administration (FDA) approved the Ebola vaccine rVSV-ZEBOV (tradename "Ervebo") as a single dose vaccine regimen against only the *Zaire ebolavirus* species of ebolavirus. This is the first FDA approval of a vaccine for Ebola.

III-228. The answer is C. *(Chap. 207)* This silver stain shows the typical small (2–5 μm) budding yeast of *Histoplasma capsulatum* on bronchoalveolar lavage (BAL). Patients receiving infliximab and other anti–tumor necrosis factor therapies are at risk of developing opportunistic infection with tuberculosis, *Histoplasma*, other pathogenic fungi (including *Pneumocystis*), *Legionella*, and viruses (including cytomegalovirus). These infections typically manifest after approximately 2 months of therapy, although shorter and longer durations are described. Patients with AIDS (CD4 <200), extremes of age, and prednisone therapy are also at risk of disseminated histoplasmosis. Disseminated histoplasmosis may present with shock, respiratory failure, pancytopenia, disseminated intravascular coagulation, and multiorgan failure or as a more indolent illness with focal organ dissemination, fever, and systemic symptoms. Cultures of bronchoalveolar fluid are positive in >50% of cases of acute respiratory histoplasmosis. Bone marrow and blood cultures have a high yield in disseminated cases. Histoplasma antigen testing of blood and BAL are also sensitive and specific. There is potential cross-reactivity with blastomycosis, coccidioidomycosis, and paracoccidioidomycosis.

III-229. The answer is E. *(Chap. 207)* Patients with severe life-threatening Histoplasma infection should be treated with a lipid formulation of amphotericin B followed by itraconazole. In immunosuppressed patients, the degree of immunosuppression should be reduced if possible. Caspofungin (and other echinocandins) is not active against *Histoplasma* but would be used for infection with *Candida* or *Aspergillus*. Ganciclovir is recommended for cytomegalovirus infection. Isoniazid/rifampin/pyrazinamide/ethambutol is recommended therapy for *Mycobacterium tuberculosis*. Clarithromycin/rifampin/ethambutol is recommended therapy for *M. avium* complex.

III-230. The answer is E. *(Chap. 208)* This patient likely has coccidioidomycosis with meningitis as evidenced by his history, physical examination, laboratory findings, and diagnostic microbes in the cerebrospinal fluid (CSF). Coccidioidomycosis is confined to the Western Hemisphere between the latitudes of 40°N and 40°S. In the United States, areas of high endemicity include the southern portion of the San Joaquin Valley of California (hence the sobriquet "Valley fever") and the south-central region of Arizona. However, infection may be acquired in other areas of the southwestern United States, including the southern coastal counties in California, southern Nevada, southwestern Utah, southern New Mexico, and western Texas (including the Rio Grande Valley). The recent acquisition of cases well outside the recognized areas, including in eastern Washington state and in northeastern Utah, suggests that the endemic region may be expanding. Clinical dissemination outside the thoracic cavity occurs in fewer than 1% of infected individuals. Dissemination is more likely to occur in male patients, particularly those of African American or Filipino ancestry, and in persons with depressed cellular immunity, including patients with HIV infection and peripheral-blood CD4+ T-cell counts of <250/μL; those receiving chronic glucocorticoid therapy; those with allogeneic solid-organ transplants; and those being treated with tumor necrosis factor-α antagonists. Coccidioidal meningitis, if untreated, is uniformly fatal. Patients usually present with a persistent headache, which is sometimes accompanied by lethargy and confusion. Nuchal rigidity, if present, is not severe. Examination of CSF demonstrates lymphocytic pleocytosis with profound hypoglycorrhachia and elevated protein levels. While once prescribed routinely, amphotericin B in all its formulations is now reserved for only the most severe cases of dissemination and for intrathecal or intraventricular administration to patients with coccidioidal meningitis in whom triazole antifungal therapy has failed. High doses of triazole antifungals are the principal drugs now used to treat most cases of coccidioidomycosis. Clinical trials have demonstrated the usefulness of both fluconazole and itraconazole. Evidence indicates that itraconazole is efficacious against bone and joint disease. Because of its demonstrated penetration into CSF, fluconazole is the azole of choice for the treatment of coccidioidal meningitis, but itraconazole also is effective. Micafungin is active against

Candida and *Aspergillus*, not coccidioidomycosis, and has poor CNS penetration. Ceftriaxone is one commonly used empiric agent for bacterial meningitis. Penicillin G is the preferred therapy for tertiary syphilis.

III-231. The answer is C. *(Chap. 208) Coccidioides immitis* is a mold that is found in the soil in the southwestern United States and Mexico. Case clusters of primary disease may appear 10–14 days after exposure, and the activities with the highest risk include archaeological excavation, rock hunting, military maneuvers, and construction work. Only 40% of primary pulmonary infections are symptomatic (Table III-231). Symptoms may include those of a hypersensitivity reaction such as erythema nodosum (typically on the lower extremities), erythema multiforme (typically in a necklace distribution), arthritis, or conjunctivitis. Blood eosinophilia is common during acute infection. While pleurisy is common, significant pleural effusion only occurs in 10% of cases (typically mononuclear with negative culture). Diagnosis can be made by culture of sputum; however, when this organism is suspected, the laboratory needs to be notified as it is a biohazard level 3 fungus. Serologic tests of blood may also be helpful; however, seroconversion of primary disease may take up to 8 weeks. Skin testing is useful only for epidemiologic studies and is not done in clinical practice.

TABLE III-231 Clinical Presentations of Coccidioidomycosis, Their Frequency, and Recommended Initial Therapy for the Immunocompetent Host

Clinical Presentation	Frequency (%)	Recommended Therapy
Asymptomatic infection	60	None
Primary pneumonia (focal)	40	In most cases, none[a]
Diffuse pneumonia	<1	Amphotericin B followed by prolonged oral triazole therapy
Pulmonary sequelae	5	
Nodule		None
Cavity		In most cases, none[b]
Chronic pneumonia		Prolonged triazole therapy
Disseminated disease	≤1	
Skin, bone, joint, soft tissue disease		Prolonged triazole therapy[c]
Meningitis		Lifelong triazole therapy[d]

[a] Treatment is indicated for hosts with depressed cellular immunity as well as for those with prolonged symptoms and signs of increased severity, including night sweats for >3 weeks, weight loss of >10%, a complement fixation titer of >1:16, and extensive pulmonary involvement on chest radiography.

[b] Treatment (usually with the oral triazoles fluconazole and itraconazole) is recommended for persistent symptoms.

[c] In severe cases, some clinicians would use amphotericin B as initial therapy.

[d] Intraventricular or intrathecal amphotericin B is recommended in cases of triazole failure. Hydrocephalus may occur, requiring a cerebrospinal fluid shunt.

Note: See text for dosages and durations.

III-232. The answer is E. *(Chap. 208)* Northern Arizona (i.e., the Grand Canyon region) is not a region of high incidence of coccidioidomycosis. Coccidioidomycosis is confined to the Western Hemisphere between the latitudes of 40°N and 40°S. In the United States, areas of high endemicity include the southern portion of the San Joaquin Valley of California and the south-central region of Arizona. However, infection may be acquired in other areas of the southwestern United States, including the southern coastal counties in California, southern Nevada, southwestern Utah, southern New Mexico, and western Texas, including the Rio Grande Valley. Outside the United States, coccidioidomycosis is endemic to northern Mexico as well as to localized regions of Central America. In South America, there are endemic foci in Colombia, Venezuela, northeastern Brazil, Paraguay, Bolivia, and north-central Argentina. Eosinophilia is a common laboratory finding in acute coccidioidomycosis, and erythema nodosum is a common cutaneous clinical feature (particularly on the lower extremities in women). Mediastinal lymphadenopathy is more commonly seen on x-rays for all acute pneumonias due to endemic mycoses, including

Coccidioides, rather than due to bacterial pneumonia. A positive complement fixation test is one method to diagnose acute infection.

III-233. The answer is D. *(Chap. 209)* Blastomycosis is caused by the dimorphic fungus, *Blastomyces dermatitidis*, which commonly resides in soil and is acquired through inhalation. Most cases of blastomycosis are reported from North America with the most common regions bordering the Mississippi and Ohio River basins, the upper Midwest and Canada bordering the Great Lakes, and a small area of New York and Ontario bordering the St. Lawrence River. Coccidioidomycosis is endemic in southern Arizona. Blastomycosis most commonly presents as acute or chronic pneumonia that has been refractory to therapy with antibacterial drugs. Whether acute or chronic, blastomycosis may mimic many other disease processes. For example, acute pulmonary blastomycosis may present with signs and symptoms indistinguishable from those of bacterial pneumonia or influenza, and chronic pulmonary blastomycosis may mimic malignancy or tuberculosis. The most common radiologic findings are alveolar infiltrates with or without cavitation, mass lesions that mimic bronchogenic carcinoma, and fibronodular infiltrates. Hematogenous dissemination to the skin, bones, and genitourinary tract occurs most often in association with chronic pulmonary disease. Skin lesions are often misdiagnosed as basal cell or squamous cell carcinoma, pyoderma gangrenosum, or keratoacanthoma. Laryngeal lesions are frequently mistaken for squamous cell carcinoma. Osteomyelitis occurs in as many as one-fourth of *B. dermatitidis* infections. The vertebrae, pelvis, sacrum, skull, ribs, and long bones are most frequently involved. Thus, the clinician must maintain a high index of suspicion and ensure that secretions or biopsy materials from patients who live in or have visited regions endemic for blastomycosis are subjected to careful histologic evaluation. This diligence is especially important in caring for individuals with pneumonia who fail to respond to treatment with antibacterial agents.

III-234. The answer is C. *(Chap. 209)* The constellation of symptoms including chronic pneumonia with ulcerating skin lesions and soil exposure in the upper Midwest in the Great Lakes region is highly suggestive of disseminated blastomycosis infection. Sputum or skin biopsy may show broad-based budding yeast. The definitive diagnosis would be made by growth of the organism from sputum or skin biopsy. An assay that detects *Blastomyces* antigen in urine and serum is commercially available and is reasonably sensitive and specific. Antigen detection appears to be more sensitive in urine than in serum. This antigen test may be useful for monitoring of patients during therapy or for early detection of relapse. A *Blastomyces* antibody enzyme immunoassay targeting the BAD-1 protein is also available. In combination with antigen testing, the sensitivity was >95% in blastomycosis patients, with 94% specificity in histoplasmosis patients. Chemiluminescent DNA probes are commonly used to confirm identification of *B. dermatitidis* once growth has been detected in culture. Repetitive sequence–based polymerase chain reaction is available. Therapy for blastomycosis in a non–life-threatening condition is with itraconazole. Lipid formulations of amphotericin are indicated in life-threatening disease or central nervous system (CNS) disease (fluconazole can also be used for CNS disease). Blastomycosis may present with solitary pulmonary lesions that may be suggestive of malignancy and should be evaluated as such. The chronic indolent form may also be confused with pulmonary tuberculosis. The differential diagnosis of blastomycosis skin lesions includes pyoderma gangrenosum that may be associated with inflammatory bowel disease. Methicillin-resistant *Staphylococcus aureus* skin lesions may be nodular and then ulcerate, but when associated with hematologic dissemination from the lung, they are usually more acute than this indolent presentation.

III-235. The answer is B. *(Chap. 210)* The goal of therapy for cryptococcal meningoencephalitis in a nonimmunosuppressed patient is cure of the fungal infection, not simply control of symptoms. Therefore, lifelong therapy is not generally necessary. Pulmonary cryptococcosis in an immunocompetent host sometimes resolves without therapy. However, given the propensity of *Cryptococcus* species to disseminate from the lung, the inability to gauge the host's immune status precisely, and the availability of low-toxicity therapy in the form of fluconazole, the current recommendation is for pulmonary cryptococcosis in an immunocompetent individual to be treated with fluconazole (200–400 mg/d for 3–6 months). Extrapulmonary cryptococcosis without central nervous system (CNS) involvement in an immunocompetent host can be treated with the same regimen, although amphotericin B (AmB; 0.5–1 mg/kg daily for 4–6 weeks) may be required for more severe cases. For CNS involvement in a host without AIDS or obvious immune impairment, most authorities recommend initial therapy with AmB (0.5–1 mg/kg daily) during an induction phase, which is followed by prolonged therapy with fluconazole (400 mg/d) during a consolidation phase. For cryptococcal meningoencephalitis without a concomitant immunosuppressive condition, the recommended regimen is AmB (0.5–1 mg/kg) plus flucytosine (100 mg/kg) daily for 6–10 weeks. Alternatively, patients can be treated with AmB (0.5–1 mg/kg) plus flucytosine (100 mg/kg) daily for 2 weeks and then with fluconazole (400 mg/d) for at least 10 weeks. Patients with immunosuppression are treated with the same initial regimens except that consolidation therapy with fluconazole is given for a prolonged period to prevent relapse. Neither caspofungin nor micafungin has activity against *Cryptococcus*. Voriconazole and posaconazole are highly active against cryptococcal strains and appear effective clinically, but clinical experience with these agents in the treatment of cryptococcosis is limited. Ceftriaxone and vancomycin are the recommended treatments for bacterial meningitis in an immunocompetent patient <50 years of age and have no role in the therapy of *Cryptococcus*.

III-236. The answer is A. *(Chap. 210)* The most likely diagnosis in this patient is cryptococcal meningitis. Visualization of the capsule of fungal cells in cerebrospinal fluid (CSF) mixed with India ink is a useful rapid diagnostic technique. Cryptococcal cells in India ink have a distinctive appearance because their capsules exclude ink particles. However, the CSF India ink examination may yield negative results in patients with a low fungal burden. This examination should be performed by a trained individual, since leukocytes and fat globules can sometimes be mistaken for fungal cells. Fungal cultures of CSF and blood that are positive for cryptococcal cells are diagnostic for cryptococcosis, but may take several days. In cryptococcal meningitis, CSF examination usually reveals evidence of chronic meningitis with mononuclear cell pleocytosis and increased protein levels. A particularly useful test is cryptococcal antigen (CRAg) detection in CSF and blood, which can return more quickly than CSF cultures. The assay is based on serologic detection of cryptococcal polysaccharide and is both highly sensitive and specific. A positive CRAg test in the CSF provides strong presumptive evidence for cryptococcosis; however, because the result is often negative in pulmonary cryptococcosis, the test is less useful in the diagnosis of pulmonary disease and is of only limited usefulness in monitoring the response to therapy. While chest imaging may reveal abnormalities, it is most urgent to make the diagnosis of meningitis.

III-237. The answer is A. *(Chap. 211)* Innate immunity is the most important defense mechanism against hematogenously disseminated candidiasis, and the neutrophil is the most important component of this defense. Macrophages also play an important defensive role. STAT1, Dectin-1, CARD9, and TH1 and TH17 lymphocytes contribute significantly to innate defense. Many clinical conditions and risk factors have been identified that are associated with hematogenous dissemination of *Candida* (Table III-237). Patients receiving antibiotics are at increased risk of developing disseminated candidiasis. The other listed conditions are not recognized as particular risk factors for disseminated candidiasis.

TABLE III-237 Well-Recognized Factors and Conditions Predisposing to Hematogenously Disseminated Candidiasis

Antibacterial agents	Abdominal and thoracic surgery
Indwelling IV catheters	Cytotoxic chemotherapy
Hyperalimentation fluids	Immunosuppressive agents for organ transplantation
Indwelling urinary catheters	Respirators
Parenteral glucocorticoids	Neutropenia
Severe burns	Low birth weight (neonates)
HIV-associated low CD4+ T-cell counts	Diabetes

III-238. The answer is D. *(Chap. 211)* This patient presents with the classic skin presentation of disseminated candidiasis. The skin lesions, severe myalgias, joint pains, and fever are typical manifestations of hematogenous spread from either a gastrointestinal or skin source in a patient predisposed by neutropenia and indwelling catheters. The severe myalgias are a characteristic of this syndrome and should be taken seriously as a new complaint in a susceptible host. Blood cultures are likely to be positive, but staining of the skin lesions is positive in virtually 100% of cases. *Candida* is the only fungus that can typically be visualized on tissue Gram stain in the form of pseudohyphae and hyphae. *Aspergillus* is seen in tissue as clumps of branching (45°) septated hyphae often with angioinvasion and necrosis. *Aspergillus* may also disseminate in a prolonged neutropenic patient, usually from a lung infection, and cause rapidly progressive skin lesions, usually with a necrotic center. *Histoplasma* and *Blastomyces* can be visualized in tissue as budding yeast. Encapsulated yeasts on India ink are indicative of *Cryptococcus*. Spherules are specific to coccidioidomycosis.

III-239. The answer is D. *(Chap. 211) Candida* species are susceptible to a number of systemic antifungal agents. Most institutions chose an agent based on their local epidemiology and resistance patterns (Table III-239). Fluconazole is the most commonly used agent for nonneutropenic hemodynamically stable patients, unless azole resistance is considered an issue. In a hemodynamically unstable neutropenic patient, more broad-spectrum agents are typically used such as polyenes, echinocandins, or later-generation azoles such as voriconazole. Lipid formulations of amphotericin, while not approved by the U.S. Food and Drug Administration as primary therapy, are commonly used because they are less toxic than amphotericin B deoxycholate. At present, the vast majority of isolates of *Candida albicans* are sensitive to fluconazole. *C. glabrata* and *C. krusei* are more sensitive to polyenes and echinocandins. Flucytosine is not used as sole therapy for *Candida*. It may be combined with amphotericin for treatment of *Candida* endophthalmitis and meningitis.

TABLE III-239 Agents for the Treatment of Disseminated Candidiasis

Agent	Route of Administration	Dose[a]	Comment
Amphotericin B deoxycholate	IV only	0.5–1.0 mg/kg daily	Being replaced by lipid formulations
Amphotericin B lipid formulations			Not approved as primary therapy by the U.S. Food and Drug Administration, but used commonly because less toxic than amphotericin B deoxycholate
Liposomal (AmBiSome, Abelcet)	IV only	3.0–5.0 mg/kg daily	
Lipid complex (ABLC)	IV only	3.0–5.0 mg/kg daily	
Colloidal dispersion (ABCD)	IV only	3.0–5.0 mg/kg daily	Associated with frequent infusion reactions
Azoles[b]			
Posaconazole	IV and oral	300 mg/d (IV) 200 mg tid (oral)	Approved for prophylaxis
Fluconazole	IV and oral	400 mg/d	Most commonly used
Voriconazole	IV and oral	400 mg/d	Multiple drug interactions Approved for candidemia in nonneutropenic patients
Echinocandins			Broad spectrum against *Candida* species; approved for disseminated candidiasis
Caspofungin	IV only	50 mg/d	
Anidulafungin	IV only	100 mg/d	
Micafungin	IV only	100 mg/d	

[a] For loading doses and adjustments in renal failure, see Pappas PG et al: Clinical practice guidelines for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis* 62:e1, 2016. The recommended duration of therapy is 2 weeks beyond the last positive blood culture and the resolution of signs and symptoms of infection.

[b] Although ketoconazole is approved for the treatment of disseminated candidiasis, it has been replaced by the newer agents listed in this table. Posaconazole has been approved for prophylaxis in neutropenic patients and for oropharyngeal candidiasis.

Abbreviations: ABCD, amphotericin B colloid dispersion; ABLC, amphotericin B lipid complex.

III-240. The answer is A. *(Chap. 211)* The use of antifungal agents to prevent *Candida* infections has been controversial, but some general principles have emerged. Most centers administer prophylactic fluconazole (400 mg/d) to recipients of allogeneic stem cell transplants. High-risk liver transplant recipients also are given fluconazole prophylaxis in most centers. The use of prophylaxis for neutropenic patients has varied considerably from center to center; many centers that elect to give prophylaxis to this population use either fluconazole (200–400 mg/d) or a lipid formulation of amphotericin B (AmBiSome; 1–2 mg/d). Caspofungin (50 mg/d) also has been recommended. Some centers have used itraconazole suspension (200 mg/d). Posaconazole (200 mg three times daily) has been approved by the U.S. Food and Drug Administration for prophylaxis in neutropenic patients; it is gaining in popularity and may replace fluconazole. Prophylaxis is sometimes given to surgical patients at very high risk. The widespread use of prophylaxis for nearly all patients in general surgical or medical intensive care units is not, and should not be, a common practice for three reasons: (1) the incidence of disseminated candidiasis is relatively low, (2) the cost–benefit ratio is suboptimal, and (3) increased resistance with widespread prophylaxis is a valid concern. Prophylaxis for oropharyngeal or esophageal candidiasis in HIV-infected patients is not recommended unless there are frequent recurrences, nor is prophylaxis generally recommended for women receiving broad-spectrum antibiotics.

III-241. The answer is C. (*Chap. 211*; https://www.idsociety.org/practice-guideline/candidiasis/) Candidemia may lead to seeding of other organs. Among nonneutropenic patients, up to 10% develop retinal lesions; therefore, it is important to perform thorough funduscopy in all patients with candidemia. Focal seeding can occur within 2 weeks of the onset of candidemia and may occur even if the patient is afebrile or the infection clears. The lesions may be unilateral or bilateral and are typically small white retinal exudates (Figure III-241). However, retinal infection may progress to retinal detachment, vitreous abscess, or extension into the anterior chamber of the eye. Patients may be asymptomatic initially but may also report blurring, ocular pain, or scotoma. Abdominal abscesses are possible but usually occur in patients recovering from profound neutropenia. Fungal endocarditis is also possible. Fungal pneumonia and pulmonary abscesses are very rare and are not likely in this patient nor are fungal meningitis or vertebral osteomyelitis.

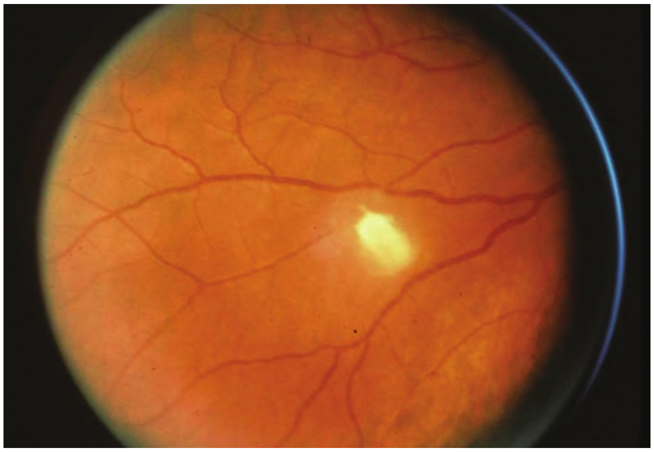


FIGURE III-241 Used with permission from Dr. Gary Holland.

III-242. The answer is A. *(Chap. 212) Aspergillus* has a worldwide distribution, most commonly growing in decomposing plant materials (i.e., compost) and in bedding. This hyaline (nonpigmented), septate, branching mold produces vast numbers of conidia (spores) on stalks above the surface of mycelial growth. Aspergilli are found in indoor and outdoor air, on surfaces, and in water from surface reservoirs. Daily exposures vary from a few to many millions of conidia; high numbers of conidia are encountered in hay barns and other very dusty environments. The required size of the infecting inoculum is uncertain; however, only intense exposures (e.g., during construction work, handling of moldy bark or hay, or composting) are sufficient to cause disease—acute community-acquired pulmonary aspergillosis—in healthy immunocompetent individuals. Allergic syndromes may be exacerbated by continuous antigenic exposure arising from sinus or airway colonization or from nail infection. High-efficiency particulate air (HEPA) filtration is often protective against infection; thus HEPA filters should be installed and monitored for efficiency in operating rooms and in areas of the hospital that house high-risk patients. The incubation period of invasive aspergillosis after exposure is highly variable, extending in documented cases from 2 to 90 days. Thus community acquisition of an infecting strain frequently manifests as invasive infection during hospitalization, although nosocomial acquisition is also common. Outbreaks usually are directly related to a contaminated air source in the hospital.

III-243. The answer is B. *(Chap. 212)* Diagnosis of invasive *Aspergillus* is often difficult because early therapy is essential and approximately 40% of cases are missed clinically and are diagnosed at autopsy. Sputum culture is positive in only 10–30% of patients, and yield is higher when fungal media rather than bacterial agar is utilized. Thus, specifically requesting fungal culture is necessary. The *Aspergillus* antigen assay relies on galactomannan release during fungal growth. Antigen testing is positive days before clinical or radiologic abnormalities appear. The sensitivity in patients with prolonged neutropenia is likely about 80%. Prior therapeutic or empiric use of antifungal therapy lowers the sensitivity of the serum test. The test can be performed on BAL samples. The CT findings in this case are also typical of the "halo sign," which is often seen in cases of invasive pulmonary aspergillosis. The halo of ground-glass infiltrate surrounding an *Aspergillus* nodule represents hemorrhagic infarction. Other fungi may cause the halo sign, but due to its tendency to be angioinvasive, *Aspergillus* is the most common. The other diagnoses in this case are much less likely given the clinical history and the radiologic signs.

III-244. The answer is E. *(Chap. 212)* Voriconazole and isavuconazole are the preferred agents for invasive aspergillosis; caspofungin, posaconazole, micafungin, and liposomal amphotericin are second-line agents. Amphotericin is not active against *Aspergillus terreus* or *A. nidulans*; multi-azole resistance in *A. fumigatus* is present in <5% of isolates but is increasing; and *A. niger* is resistant to itraconazole and isavuconazole. An infectious disease consultation is advised for patients with invasive disease, given the complexity of management. Immune reconstitution can complicate recovery. The duration of therapy for invasive aspergillosis varies from ~3 months to several years, depending on the patient's immune status and response to therapy. Relapse occurs if the response is suboptimal and immune reconstitution is not complete.

III-245. The answer is A. *(Chap. 212)* This patient has features of allergic bronchopulmonary aspergillosis (ABPA). In almost all cases, ABPA represents a hypersensitivity reaction to *Aspergillus fumigatus*; rare cases are due to other aspergilli and other fungi. ABPA occurs in ~2.5% of patients with asthma who are referred to secondary care and in up to 15% of teenagers with cystic fibrosis. Episodes of bronchial obstruction with mucous plugs leading to coughing fits, "pneumonia," consolidation, and breathlessness are typical. Many patients report coughing up thick sputum casts. It is also characterized by intermittent wheezing, bilateral pulmonary infiltrates, and brownish sputum. The cardinal diagnostic test is detection of serum *Aspergillus*-specific IgE (or a positive skin-prick test in response to *A. fumigatus* extract) together with an elevated serum level of total IgE (usually >1000 IU/mL). The presence of hyperattenuated mucus in airways is highly specific. Bronchiectasis is characteristic, and some patients develop chronic cavitary pulmonary aspergillosis, although this is not a common feature.

III-246. The answer is C. *(Chap. 212)* The patient has symptoms, imaging, and microbiological findings concerning for chronic cavitary pulmonary aspergillosis (CPA). The hallmark of chronic CPA (also called semi-invasive aspergillosis, chronic necrotizing aspergillosis, or complex aspergilloma) is one or more pulmonary cavities expanding over a period of months or years in association with pulmonary symptoms and systemic manifestations such as fatigue and weight loss. Often mistaken initially for tuberculosis, more than 90% of CPA cases occur in patients with prior pulmonary disease (e.g., tuberculosis, atypical mycobacterial infection, sarcoidosis, rheumatoid lung disease, pneumothorax, bullae) or lung surgery. The onset is insidious, and systemic features may be more prominent than pulmonary symptoms. Cavities may have a fluid level or a well-formed fungal ball, but peri-cavitary infiltrates and multiple cavities—with or without pleural thickening—are typical. An irregular internal cavity surface and thickened cavity walls are indicative of disease activity. CPA is usually caused by *Aspergillus fumigatus*, but *A. niger* has been implicated, particularly in diabetic patients, and is linked to oxalosis with renal dysfunction. IgG antibodies to *Aspergillus* are detectable in ~95% of patients with CPA. Some patients have concurrent infections—even without a fungal ball—with atypical mycobacteria and/or other bacterial pathogens. The most significant complication is life-threatening hemoptysis, which may be the presenting manifestation. Itraconazole is currently the preferred oral agent for chronic and allergic forms of aspergillosis. Voriconazole or posaconazole can be substituted when failure, emergence of resistance, or adverse events occur. An itraconazole dose of 200 mg twice daily is recommended, with monitoring of drug concentrations in the blood. Acute exacerbations of allergic bronchopulmonary aspergillosis respond well to a short course of glucocorticoids. Because chronic CPA responds slowly, therapy for >6 months is necessary, and disease control may require years of treatment, whereas the duration of treatment for other forms of chronic and allergic aspergillosis requires case-by-case evaluation. Glucocorticoids should be used in chronic cavitary pulmonary aspergillosis only if covered by adequate antifungal therapy. Antifungal response in *Aspergillus* bronchitis is gratifying, but relapse after 4 months of therapy is common.

III-247. The answer is B. *(Chap. 213)* Mucormycosis refers to life-threatening infection due to the Mucorales (formerly known as Zygomycetes) family of fungi. The most common fungus accounting for these infections is *Rhizopus oryzae*. The mortality of these infections approaches 50%. The Mucorales are environmentally ubiquitous; infection requires a defect in the patient's ability to kill the fungus or phagocytic function. The most common predisposing factors are diabetes, glucocorticoid therapy, neutropenia, or iron overload. Free iron supports fungal growth in serum and tissues, enhancing survival and virulence. Deferoxamine therapy predisposes to fatal infection because the chelator acts as a siderophore, directly delivering iron to the fungi. Acidosis also causes dissociation of iron from serum proteins, promoting growth of Mucorales. Patients with diabetic ketoacidosis are at particularly high risk of developing rhinocerebral mucormycosis likely due to the combination of acidosis and phagocytic defects associated with hyperglycemia. Hypoglycemia is not an identified risk factor for mucormycosis.

III-248. The answer is E. *(Chap. 213)* This patient has evidence of invasive rhinocerebral mucormycosis with risk factors including acute and chronic hyperglycemia and metabolic acidosis due to chronic renal insufficiency. With a greater than 50% mortality, therapy of rhinocerebral mucormycosis requires early diagnosis, reversal of underlying predisposing conditions, surgical debridement, and immediate antifungal therapy (Table III-248). Insulin and hemodialysis should be initiated to correct hyperglycemia and metabolic acidosis. Amphotericin products remain the treatment of choice for mucormycosis. Liposomal amphotericin has improved central nervous system penetration compared with the lipid complex formations. Surgical debridement is also an important component of early therapy. If untreated, the infection quickly spreads from the ethmoid sinus to the orbit and into the cavernous sinus. Development of contralateral infection suggests cavernous sinus thrombosis and portends a very poor prognosis. Differentiation of mucormycosis from *Aspergillus* is important because *Aspergillus* species tend to infect similar hosts and are rapidly fatal. In contrast to mucormycosis species, the hyphae of *Aspergillus* species are septated, are thinner, and branch at acute angles. Voriconazole, the initial therapy for *Aspergillus*, is not indicated in mucormycosis and, in fact, has been shown to exacerbate mucormycosis in animal models. Echinocandin antifungal agents have activity against Mucorales in combination with lipid polyene agents.

TABLE III-248 Antifungal Options for the Treatment of Mucormycosis[a]

Drug	Recommended Dosage	Advantages and Supporting Studies	Disadvantages
First-Line Antifungal Therapy			
AmB deoxycholate	1.0–1.5 mg/kg once per day	• >5 decades of clinical experience • Inexpensive • FDA-approved for treatment of mucormycosis	• Highly toxic • Poor CNS penetration
LAmB	5–10 mg/kg once per day	• Less nephrotoxic than AmB deoxycholate • Better CNS penetration than AmB deoxycholate or ABLC • Better outcomes than with AmB deoxycholate in murine models and a retrospective clinical review	• Expensive
ABLC	5 mg/kg once per day	• Less nephrotoxic than AmB deoxycholate • Murine and retrospective clinical data suggest benefit of combination therapy with echinocandins	• Expensive • Possibly less efficacious than LAmB for CNS infection
Second-Line/Salvage Option			
Isavuconazole	200 mg of isavuconazole (372 mg of isavuconazonium sulfate), load q8h × 6 followed by once-daily dosing	• Efficacy similar to that of LAmB in mouse models • FDA-approved for treatment of mucormycosis • May be a rational empirical option when septate mold vs mucormycosis is not yet established	• Much less clinical experience; concern about a more slowly cidal agent than lipid polyenes • Clinical study supporting approval was small and historically controlled
Posaconazole	200 mg qid	• In vitro activity against the Mucorales, with lower MICs than isavuconazole • Retrospective data for salvage therapy in mucormycosis	• Substantially lower blood levels than isavuconazole • No data on initial therapy for mucormycosis, and no evidence for combination therapy with posaconazole • Experience limited, potential use for salvage therapy
Combination Therapy[b]			
Echinocandin plus lipid polyene	Standard echinocandin doses	• Favorable toxicity profile • Synergistic in murine disseminated mucormycosis • Retrospective clinical data suggest superior outcomes for rhino-orbital-cerebral mucormycosis.	• Limited clinical data on combination therapy
Lipid polyene plus azole (posaconazole or isavuconazole)	Standard doses	• Favorable toxicity profile	• Limited efficacy data, with no available evidence of superiority vs monotherapy
Triple therapy (lipid polyene plus echinocandin plus azole)	Standard doses	• Maximal aggressiveness	• Limited efficacy data, with no available evidence for superiority vs monotherapy or dual therapy

[a] Primary therapy should generally include a polyene. Non–polyene-based regimens may be appropriate for patients who refuse polyene therapy or for relatively immunocompetent patients with mild disease (e.g., isolated suprafascial cutaneous infection) that can be surgically eradicated.

[b] Prospective randomized trials are necessary to confirm the suggested benefit (from animal and small retrospective human studies) of combination therapy for mucormycosis. Dose escalation of any echinocandin is not recommended because of a paradoxical loss of benefit of combination therapy at echinocandin doses of ≥3 mg/kg per day.

Abbreviations: ABLC, AmB lipid complex; AmB, amphotericin B; CNS, central nervous system; FDA, U.S. Food and Drug Administration; LAmB, liposomal AmB; MIC, minimal inhibitory concentration.

Source: Data from Spellberg B et al: Recent advances in the management of mucormycosis: from bench to bedside. *Clin Infect Dis* 48:174, 2009.

III-249. The answer is E. *(Chap. 214)* This patient has tinea capitis most likely caused by the dermatophytic mold, *Trichophyton*. The other dermatophytes that less frequently cause cutaneous infection include *Microsporum* and *Epidermophyton*. They are not part of the normal skin flora but can live in keratinized skin structures. Infections with these organisms are extremely common and are often called ringworm, although the causative organisms are fungi not worms. They manifest as infection of the head (tinea capitis), feet (tinea pedis), crotch (tinea cruris), and nails (tinea unguium or onychomycosis). Tinea capitis is most common in children age 3–7 but also occurs in adults. Usually, the typical appearance, as in this case, is diagnostic. Scrapings may be taken from the edge of the lesion and stained with KOH to reveal hyphae. Dermatophyte infections often respond to topical therapy. For troublesome infections, itraconazole or terbinafine for 1–2 weeks can hasten resolutions. Terbinafine is often preferred because of fewer drug interactions.

III-250. The answer is B. *(Chap. 214)* Tinea versicolor is the most common superficial skin infection. It is caused by lipophilic yeasts of the genus *Malassezia*, most commonly *M. furfu*r. In tropical areas, the prevalence of tinea versicolor is 40–60%, whereas in temperate areas, it is about 1%. In general, most individuals seek evaluation for cosmetic reasons as the lesions in tinea versicolor are asymptomatic or only mildly pruritic. The lesions typically appear as patches of pink or coppery-brown skin, but the areas may be hypopigmented in dark-skinned individuals. Diagnosis can be made by demonstrating the organism on potassium hydroxide preparation where a typical "spaghetti and meatballs" appearance may be seen. This is due to the presence of both spore forms and hyphal forms within the skin. Under long-wave ultraviolet A light (Wood lamp), the affected areas fluoresce to yellow-green. The organism is sensitive to a variety of antifungals. Selenium sulfide shampoo, topical azoles, terbinafine, and ciclopirox have all been used with success. A 2-week treatment regimen typically shows good results, but the infection typically recurs within 2 years of initial treatment. *Fusarium solani* is an environmental fungus that usually causes infection in immunocompromised hosts. It can cause keratitis, onychomycosis, pneumonia, and hematogenous dissemination. *Sporothrix schenckii* is the usual etiologic agent of sporotrichosis. *Penicillium marneffei* is endemic in Vietnam, Thailand, and other Southeast Asian countries. It causes a clinical syndrome similar to disseminated Histoplasmosis, particularly in immunocompromised patients. *Trichophyton rubrum* is a dermatophyte that causes ringworm.

III-251. The answer is C. *(Chap. 214)* The patient has sporotrichosis, caused by *Sporothrix schenckii*. Sporotrichosis most commonly affects persons who participate in outdoor activities such as landscaping, gardening, and tree farming. Sporotrichosis is primarily a localized infection of skin and subcutaneous tissues that follows traumatic inoculation of conidia. Days or weeks after inoculation, a papule develops at the site and then usually ulcerates but is not very painful. Similar lesions develop sequentially along the lymphatic channels proximal to the original lesion. Some patients develop a fixed cutaneous lesion that can be verrucous or ulcerative and that remains localized without lymphatic extension. The differential diagnosis of lymphocutaneous sporotrichosis includes nocardiosis, tularemia, nontuberculous mycobacterial infection (especially that due to *Mycobacterium marinum*), and leishmaniasis. *S. schenckii* usually grows readily as a mold on Sabouraud agar when material from a cutaneous lesion is incubated at room temperature. Histopathologic examination of biopsy material shows a mixed granulomatous and pyogenic reaction, and tiny oval or cigar-shaped yeasts sometimes can be seen with special stains. In cases in which the organism has not grown, polymerase chain reaction of tissue samples can sometimes be helpful. Guidelines for the management of the various forms of sporotrichosis have been published by the Infectious Diseases Society of America (Table III-251). Itraconazole is the drug of choice for lymphocutaneous sporotrichosis. Fluconazole is less effective, voriconazole is not effective, and posaconazole has been used successfully in a few instances. Saturated solution of potassium iodide (SSKI) continues to be used for lymphocutaneous infection because it costs much less than itraconazole. However, SSKI is poorly tolerated because of adverse reactions, including metallic taste, salivary gland swelling, rash, and fever. High-dose terbinafine may be effective for lymphocutaneous infection. Treatment for lymphocutaneous sporotrichosis is continued for 2–4 weeks after all lesions have resolved, usually for a total of 3–6 months. The success rate for treatment of lymphocutaneous sporotrichosis is 90–100%. Trimethoprim-sulfamethoxazole is the treatment of choice for nocardiosis. Clarithromycin with ethambutol is the treatment of choice for uncomplicated *M. marinum* infection.

TABLE III-251 Suggested Treatment for Endemic Mycoses

Disease	First-Line Therapy	Alternatives/Comments
Sporotrichosis		
Cutaneous, lymphocutaneous	Itraconazole, 200 mg/d until 2–4 weeks after lesions resolve	SSKI, increasing doses[a] Terbinafine, 500 mg bid
Pulmonary, osteoarticular	Itraconazole, 200 mg bid for 12 months	Lipid AmB[b] for severe pulmonary disease until stable; then itraconazole
Disseminated, central nervous system	Lipid AmB[b] for 4–6 weeks	Itraconazole, 200 mg bid after AmB for 12 months AIDS patients: itraconazole maintenance, 200 mg/d until CD4+ T-cell count is >200/μL for ≥12 months
Paracoccidioidomycosis		
Chronic (adult form)	Itraconazole, 100–200 mg/d for 6–12 months	Voriconazole, 200 mg bid for 6–12 months Posaconazole, 300 mg/d for 6–12 months TMP-SMX, 160/800 mg bid for 12–36 months
Acute (juvenile form)	AmB[c] or lipid AmB[b] until improvement	Itraconazole, 200 mg bid after AmB for 12 months Voriconazole or posaconazole at doses noted above may be used
Talaromycosis (Penicilliosis)		
Mild or moderate	Itraconazole, 200 mg bid for 12 weeks	Voriconazole, 200 mg bid
Severe	Lipid AmB[b] or AmB[c] until improvement	Itraconazole, 200 mg bid after AmB for 12 weeks
Maintenance therapy (AIDS)	200 mg/d until CD4+ T-cell count is >100/μL for ≥6 months	

[a] The starting dosage is 5–10 drops tid in water or juice. The dosage is increased weekly by 10 drops per dose, as tolerated, up to 40–50 drops tid.

[b] The dosage of lipid AmB is 3–5 mg/kg daily; the higher dosage should be used when the central nervous system is involved.

[c] The dosage of AmB deoxycholate is 0.6–1.0 mg/kg daily.

Abbreviations: AmB, amphotericin B; SSKI, saturated solution of potassium iodide; TMP-SMX, trimethoprim-sulfamethoxazole.

III-252. The answer is C. *(Chap. 215)* The CT image shows bilateral symmetric ground-glass and interstitial infiltrates consistent with *Pneumocystis jiroveci* pneumonia (PJP). Patients receiving biologic agents, including the tumor necrosis factor antagonists infliximab and etanercept, are at increased risk of multiple infections including pneumocystis. *Pneumocystis* is thought to be a worldwide organism with most people exposed before 5 years of age. Airborne transmission has been demonstrated in animal studies, and epidemiologic studies suggest person-to-person transmission in nosocomial settings. Patients with defects in cell and humoral immunity are at risk of developing pneumonia. Most cases are in HIV-infected patients with CD4 counts <200/μL. Others at risk include patients receiving immunosuppressive agents (particularly glucocorticoids) for cancer or organ transplantation, children with immunodeficiency, premature malnourished infants, and patients receiving biologic immunomodulating agents. PJP typically presents in non–HIV-infected patients with several days of dyspnea, fever, and nonproductive cough. Often, symptoms develop during or soon after a glucocorticoid taper. *Pneumocystis* is associated with a reduced diffusing capacity on pulmonary function that will typically cause mild hypoxemia and significant oxygen desaturation with exertion. Chest radiography will often show bilateral diffuse infiltrates without pleural effusion. Early in the disease, the radiograph may be unremarkable, but chest CT will show diffuse ground-glass infiltrates as in this case. Patients receiving biologic agents are at risk of pneumonia due to tuberculosis (the patient in this case was on prophylaxis), *Aspergillus*, and *Nocardia*. *Aspergillus*, *Nocardia*, and septic emboli typically appear as nodules on chest CT. Rheumatoid nodules would be unlikely in the context of improving joint disease.

III-253. The answer is A. *(Chap. 215)* The most effective method for preventing *Pneumocystis jiroveci* pneumonia (PJP) is to eliminate the cause of immunosuppression by withdrawing immunosuppressive therapy or treating the underlying cause (e.g., HIV infection). Patients who are susceptible to PJP benefit from chemoprophylaxis during the period of susceptibility. For patients with HIV infection, CD4+ T-cell counts are a reliable marker of susceptibility, and counts below 200/μL are an indication to start prophylaxis. It is clearly indicated in HIV-infected patients with oropharyngeal candidiasis or CD4 count <200/μL and in HIV-infected or non–HIV-infected patients with a history of prior PJP.

Prophylaxis may be discontinued in HIV-infected patients who respond to therapy once the CD4 count has risen to >200/μL for >3 months. For patients who are immunosuppressed as a result of factors other than HIV infection, there is no laboratory parameter, including the CD4+ T-cell count, that predicts susceptibility to PJP with adequate positive and negative accuracy. The period of susceptibility is usually estimated on the basis of experience with the underlying disease and immunosuppressive regimen. Premature cessation of prophylaxis has been associated with clusters of cases in certain patient populations, such as solid-organ transplant recipients. Patients receiving a prolonged course of high-dose glucocorticoids appear to be particularly susceptible to PJP. The glucocorticoid exposure threshold that warrants chemoprophylaxis is controversial, but such preventive therapy should be strongly considered for any patient who is receiving more than the equivalent of 20 mg of prednisone daily for 30 days or who is receiving glucocorticoids in conjunction with other immunosuppressive agents. Clinical experience also suggests that chemoprophylaxis is useful for patients receiving certain immunosuppressive agents (e.g., tumor necrosis factor inhibitors, antithymocyte globulin, rituximab, and alemtuzumab). The duration of such chemoprophylaxis is empirically determined by clinical and laboratory indicators of immunologic vulnerability. Short courses of corticosteroids, such as during an asthma exacerbation, do not warrant PJP prophylaxis in the absence of a prior history.

III-254. The answer is B. *(Chap. 215)* The treatment of choice for *Pneumocystis jiroveci* pneumonia (PJP) is trimethoprim-sulfamethoxazole (TMP-SMX), given either IV or PO for 14 days to non–HIV-infected patients with mild disease and for 21 days to all other patients. TMP-SMX, which interferes with the organism's folate metabolism, is at least as effective as alternative agents and is better tolerated. TMP-SMX can cause leukopenia, hepatitis, rash, and fever as well as anaphylactic and anaphylactoid reactions, and patients with HIV infection have an unusually high incidence of hypersensitivity to TMP-SMX. Monitoring of serum drug levels is useful if renal function or toxicities are issues. Maintenance of a 2-hour post-dose serum SMX level of 100–150 μg/mL has been associated with a successful outcome. Resistance to TMP-SMX cannot be measured by organism growth inhibition in the laboratory because *Pneumocystis* cannot be cultured. However, mutations in the target gene for SMX that confer in vitro sulfa resistance to other organisms have been found in *Pneumocystis*. The clinical relevance of these mutations for the response to therapy is unknown. Sulfadiazine plus pyrimethamine, an oral regimen more often used for treatment of toxoplasmosis, also is highly effective. Dapsone plus pyrimethamine or dapsone plus TMP also can be used. IV pentamidine or the combination of clindamycin plus primaquine is an option for patients who cannot tolerate TMP-SMX and for patients in whose treatment TMP-SMX appears to be failing. Pentamidine must be given IV over at least 60 minutes to avoid potentially lethal hypotension. Adverse effects can be severe and irreversible and include renal dysfunction, dysglycemia (life-threatening hypoglycemia that can occur days or weeks after initial infusion and be followed by hyperglycemia), neutropenia, and torsades des pointes. Clindamycin plus primaquine is effective, but primaquine can be given only by the oral route—a disadvantage for patients who cannot ingest or absorb oral drugs. Oral atovaquone is also a reasonable option for patients with mild disease who have no impediments to absorbing an oral drug that requires a high-fat meal for optimal absorption. A major advance in therapy for PJP was the recognition that glucocorticoids could improve survival rates among HIV-infected patients with moderate to severe disease (room air PO_2, <70 mmHg; or alveolar–arterial oxygen gradient, ≥35 mmHg). Glucocorticoids appear to reduce the pulmonary inflammation that occurs after specific therapy is started and organisms begin to die, eliciting inflammation. Therapy with glucocorticoids should be the standard of care for patients with HIV infection and probably is also effective for patients with other immunodeficiencies. This treatment should be started for moderate or severe disease when therapy for PJP is initiated, even if the diagnosis has not yet been confirmed. If HIV-infected or HIV-uninfected patients are receiving high-dose glucocorticoids when they develop PJP, there are theoretical advantages to either increasing the steroid dose (to reduce the inflammatory response to the dying organisms) or decreasing the steroid dose (to improve immune function), but there is no convincing evidence on which to base any specific strategy.

III-255. The answer is E. *(Chap. 218)* CT scan demonstrates a large amebic abscess in the right lobe of the liver. *Entamoeba histolytica* is a common pathogen in areas of the world with poor sanitation and crowding. It is endemic in Mexico and Central America as well as in India, tropical Asia, and Africa. Transmission is oral-fecal, and the primary manifestation is colitis, which is often heme-positive. Liver abscess is a common complication, occurring after the organism crosses the colonic border and travels through the portal circulation, subsequently lodging in the liver. At the time of presentation with liver abscess, the primary gastrointestinal infection has usually cleared and organisms cannot be identified in the stool. Enzyme-linked immunosorbent assays and agar gel diffusion assays are positive in more than 90% of patients with colitis, amebomas, or liver abscess. Positive results in conjunction with the appropriate clinical syndrome suggest active disease because serologic findings usually revert to negative within 6–12 months. Up to 10% of patients with acute amebic liver abscess may have a negative serologic funding; in suspected cases with an initially negative result, testing should be repeated in 1 week. A liver biopsy is usually not necessary. Even in highly endemic areas such as South Africa, fewer than 10% of asymptomatic individuals have a positive amebic serology. The interpretation of the indirect hemagglutination test is more difficult because titers may remain positive for as long as 10 years. Treatment for amebic liver abscess is generally with metronidazole plus a luminal agent such as paromomycin or iodoquinol. *Campylobacter* is a major cause of foodborne infectious diarrhea. While usually self-limited, it may cause serious enteritis and inflammatory diarrhea, but not liver abscess.

III-256. The answer is B. (*Chap. 219*, https://www.cdc.gov/malaria/diagnosis_treatment/artesunate.html). This patient has severe falciparum malaria. The thin smear shows trophozoites in erythrocytes and pigment in polymorphonuclear cells. Malaria is a common cause of fever in tropical countries. Appropriately and promptly treated, uncomplicated falciparum malaria (i.e., that in which the patient can sit or stand unaided and can swallow medicines and food) carries a mortality rate of <0.1%. However, once vital-organ dysfunction occurs or the total proportion of erythrocytes infected increases to >2% (a level corresponding to $>10^{12}$ parasites in an adult), mortality risk rises steeply, depending on the immunity of the host. Coma is a characteristic and ominous feature of falciparum malaria and, even with treatment, has been associated with death rates of ~20% among adults and 15% among children. Any obtundation, delirium, or abnormal behavior in falciparum malaria should be taken very seriously. The onset of coma may be gradual or sudden following a convulsion. In large randomized controlled clinical trials, parenteral artesunate, a water-soluble artemisinin derivative, has reduced mortality rates in severe falciparum malaria among Asian adults and children by 35% and among African children by 22.5% compared with quinine treatment. It is simple to administer, safe, and very effective. Artesunate therefore is now the drug of choice for all patients with severe malaria everywhere. Artesunate is given by IV injection but is also absorbed rapidly following IM injection. Artemether and the closely related drug artemotil (arteether) are oil-based formulations given by IM injection; they are erratically absorbed and do not confer the same survival benefit as artesunate. Although the artemisinin compounds are safer than quinine and considerably safer than quinidine, only one formulation is available in the United States. IV artesunate has been approved by the U.S. Food and Drug Administration; however, until it is commercially available, it can be obtained through the Centers for Disease Control and Prevention Drug Service. Quinidine has now been discontinued by the manufacturer. Severe falciparum malaria constitutes a medical emergency requiring intensive nursing care and careful management. In severe malaria, parenteral antimalarial treatment should be started immediately. If safe and feasible, exchange transfusion may be considered for patients with severe malaria, although the precise indications for this procedure have not been agreed on and there is no clear evidence that this measure is beneficial, particularly with artesunate treatment. Mefloquine should be avoided as a follow-on treatment for severe malaria because of the increased risk of post-malaria neurological syndrome.

III-257. The answer is E. *(Chap. 219)* Thick and thin smears are a critical part of the evaluation of fever in a person with recent time spent in a *Plasmodium*-endemic region. Thick smears take a longer time to process but increase sensitivity in the setting of low parasitemia. Thin smears are more likely to allow for precise morphologic evaluation to differentiate between the four different types of *Plasmodium* infection and also allow for prognostic calculation of parasitemia. The relationship between parasitemia and prognosis is complex; in general, patients with >100,000 parasites/μL are at increased risk of dying, but nonimmune patients may die with much lower counts, and partially immune persons may tolerate parasitemia levels many times higher with only minor symptoms. In severe malaria, a poor prognosis is indicated by a predominance of more mature *P. falciparum* parasites (i.e., >20% of parasites with visible pigment) in the peripheral blood film or by the presence of phagocytosed malarial pigment in >5% of neutrophils. If clinical suspicion is high, repeat smears should be performed if initially negative. If personnel are not available to rapidly interpret a smear, empirical therapy should be strongly considered to ward off the most severe manifestation of *P. falciparum* infection. Rapid, simple, sensitive, and specific antibody-based diagnostic stick or card tests that detect *P. falciparum*–specific, histidine-rich protein 2 (PfHRP2), lactate dehydrogenase, or aldolase antigens in finger-prick blood samples are now being used widely in control programs. Some of these rapid diagnostic tests carry a second antibody (either pan-malaria or *P. vivax* specific) and so distinguish falciparum malaria from the less dangerous malarias. PfHRP2-based tests may remain positive for several weeks after acute infection. This prolonged positivity is a disadvantage in high-transmission areas where infections are frequent, but it is of value in the diagnosis of severe malaria in patients who have taken antimalarial drugs and cleared peripheral parasitemia but who still have a strongly positive PfHRP2 test. A disadvantage of rapid tests is that they do not quantify parasitemia. Molecular diagnosis by polymerase chain reaction (PCR) amplification of parasite nucleic acid is more sensitive than microscopy or rapid diagnostic tests for detecting malaria parasites and defining malarial species. While currently impractical in the standard clinical setting, PCR is used in reference centers in endemic areas.

III-258. The answer is C. *(Chap. 219)* This patient is at risk of acquiring malaria. Recommendations for malaria prophylaxis depend on knowledge of local patterns of drug sensitivity in *Plasmodium* species and the likelihood of acquiring malarial infection (Table III-258). When there is uncertainty, drugs effective against resistant *P. falciparum* should be used (atovaquone-proguanil [Malarone], doxycycline, or mefloquine). Chemoprophylaxis is never entirely reliable, and malaria should always be considered in the differential diagnosis of fever in patients who have traveled to endemic areas, even if they are taking prophylactic antimalarial drugs. Travelers should start taking antimalarial drugs 2 days to 2 weeks before departure so that any untoward reactions can be detected before travel and so that therapeutic antimalarial blood concentrations will be present if and when any infections develop. Antimalarial prophylaxis should continue for 4 weeks after the traveler has left the endemic area, except if atovaquone-proguanil or primaquine has been taken; these drugs have significant activities against the liver stage of the infection (causal prophylaxis) and can be discontinued 1 week after departure from the endemic area. If suspected malaria develops while a traveler is abroad, obtaining a reliable diagnosis and antimalarial treatment locally is a top priority. Presumptive self-treatment for malaria with atovaquone-proguanil (for 3 consecutive days) or one of the artemisinin-based combinations can be considered under special circumstances; medical advice on self-treatment should be sought before departure for malaria-endemic areas and as soon as possible after illness begins. Every effort should be made to confirm the diagnosis. Atovaquone-proguanil (Malarone; 3.75/1.5 mg/kg or 250/100 mg, daily adult dose) is a fixed-combination, once-daily prophylactic agent that is very well tolerated by adults and children. This combination is effective against all types of malaria, including multidrug-resistant falciparum malaria. It is not recommended if the estimated glomerular filtration rate is <30 mL/min. Mefloquine (250 mg of salt weekly, adult dose) has been widely used for malarial prophylaxis because it is usually effective against multidrug-resistant falciparum malaria and is reasonably well tolerated. Mefloquine has been associated with rare episodes of psychosis and seizures at prophylactic doses; these reactions are more frequent at the higher doses used for treatment. More common side effects with prophylactic doses

TABLE III-258 Drugs Used in the Prophylaxis of Malaria

Drug	Usage	Adult Dose	Pediatric Dose	Comments
Atovaquone-proguanil (Malarone)	Prophylaxis in areas with chloroquine- or mefloquine-resistant *Plasmodium falciparum*	1 adult tablet PO[a]	5–8 kg: ½ pediatric tablet[b] daily ≥8–10 kg: ¾ pediatric tablet daily ≥10–20 kg: 1 pediatric tablet daily ≥20–30 kg: 2 pediatric tablets daily ≥30–40 kg: 3 pediatric tablets daily ≥40 kg: 1 adult tablet daily	Begin 1–2 days before travel to malarious areas. Take daily at the same time each day while in the malarious areas and for 7 days after leaving such areas. Atovaquone-proguanil is contraindicated in persons with severe renal impairment (creatinine clearance rate, <30 mL/min). In the absence of data, it is not recommended for children weighing <5 kg, pregnant women, or women breastfeeding infants weighing <5 kg. Atovaquone-proguanil should be taken with food or a milky drink.
Chloroquine phosphate (Aralen and generic)	Prophylaxis only in areas with chloroquine-sensitive *P. falciparum*[c] or areas with *P. vivax* only	300 mg of base (500 mg of salt) PO once weekly	5 mg of base/kg (8.3 mg of salt/kg) PO once weekly, up to maximum adult dose of 300 mg of base	Begin 1–2 weeks before travel to malarious areas. Take weekly on the same day of the week while in the malarious areas and for 4 weeks after leaving such areas. Chloroquine phosphate may exacerbate psoriasis.
Doxycycline (many brand names and generic)	Prophylaxis in areas with chloroquine- or mefloquine-resistant *P. falciparum*[c]	100 mg PO qd (except in pregnant women; see Comments)	≥8 years of age: 2 mg/kg, up to adult dose	Begin 1–2 days before travel to malarious areas. Take daily at the same time each day while in the malarious areas and for 4 weeks after leaving such areas. Doxycycline is contraindicated in children aged <8 years and in pregnant women after 15 weeks of gestation.
Hydroxychloroquine sulfate (Plaquenil)	An alternative to chloroquine for primary prophylaxis only in areas with chloroquine-sensitive *P. falciparum*[c] or areas with *P. vivax* only	310 mg of base (400 mg of salt) PO once weekly	5 mg of base/kg (6.5 mg of salt/kg) PO once weekly, up to maximum adult dose of 310 mg of base	Begin 1–2 weeks before travel to malarious areas. Take weekly on the same day of the week while in the malarious areas and for 4 weeks after leaving such areas. Hydroxychloroquine may exacerbate psoriasis.
Mefloquine (Lariam and generic)	Prophylaxis in areas with chloroquine-resistant *P. falciparum*[c]	228 mg of base (250 mg of salt) PO once weekly	≤9 kg: 4.6 mg of base/kg (5 mg of salt/kg) PO once weekly 10–19 kg: ¼ tablet[d] once weekly 20–30 kg: ½ tablet once weekly 31–45 kg: ¾ tablet once weekly ≥46 kg: 1 tablet once weekly	Begin 1–2 weeks before travel to malarious areas. Take weekly on the same day of the week while in the malarious areas and for 4 weeks after leaving such areas. Mefloquine is contraindicated in persons allergic to this drug or related compounds (e.g., quinine and quinidine) and in persons with active or recent depression, generalized anxiety disorder, psychosis, schizophrenia, other major psychiatric disorders, or seizures. Use with caution in persons with psychiatric disturbances or a history of depression. Mefloquine is not recommended for persons with cardiac conduction abnormalities.
Primaquine	For prevention of malaria in areas with mainly *P. vivax*	30 mg of base (52.6 mg of salt) PO qd	0.5 mg of base/kg (0.8 mg of salt/kg) PO qd, up to adult dose; should be taken with food	Begin 1–2 days before travel to malarious areas. Take daily at the same time each day while in the malarious areas and for 7 days after leaving such areas. Primaquine is contraindicated in persons with G6PD deficiency. It is also contraindicated during pregnancy.
Primaquine	Used for presumptive anti-relapse therapy (terminal prophylaxis) to decrease risk of relapses of *P. vivax* and *P. ovale*	30 mg of base (52.6 mg of salt) PO qd for 14 days after departure from the malarious area	0.5 mg of base/kg (0.8 mg of salt/kg), up to adult dose, PO qd for 14 days after departure from the malarious area	This therapy is indicated for persons who have had prolonged exposure to *P. vivax* and/or *P. ovale*. It is contraindicated in persons with G6PD deficiency as well as during pregnancy.

[a] An adult tablet contains 250 mg of atovaquone and 100 mg of proguanil hydrochloride.

[b] A pediatric tablet contains 62.5 mg of atovaquone and 25 mg of proguanil hydrochloride.

[c] Very few areas now have chloroquine-sensitive malaria.

[d] One tablet contains 228 mg of base (250 mg of salt).

Abbreviation: G6PD, glucose-6-phosphate dehydrogenase.

Source: Data from Centers for Disease Control and Prevention. Available from www.cdc.gov/malaria/travelers/drugs.html. Accessed December 14, 2020.

of mefloquine include mild nausea, dizziness, fuzzy thinking, disturbed sleep patterns, vivid dreams, dysphoria, and malaise. Mefloquine is contraindicated for use by travelers with known hypersensitivity and by persons with active or recent depression, anxiety disorder, psychosis, schizophrenia, another major psychiatric disorder, or seizures; it is not recommended for persons with cardiac conduction abnormalities although the evidence that it is cardiotoxic is very weak. Daily administration of doxycycline (100 mg daily, adult dose) is an effective alternative to atovaquone-proguanil or mefloquine. Doxycycline is generally well tolerated but may cause vulvovaginal thrush, diarrhea, and photosensitivity and is not recommended for prophylaxis in children <8 years old or pregnant women after 15 weeks of gestation. Chloroquine can no longer be relied on to prevent *P. falciparum* infections in most areas but is still used to prevent and treat malaria due to the other human *Plasmodium* species and for *P. falciparum* malaria in Central American countries west and north of the Panama Canal and in Caribbean countries. Chloroquine-resistant *P. vivax* has been reported from parts of eastern Asia, Oceania, and Central and South America. Primaquine (0.5 mg of base/kg or a daily adult dose of 30 mg taken with food), an 8-aminoquinoline compound, has proved safe and effective in the prevention of drug-resistant falciparum and vivax malaria in adults. Primaquine should not be given to glucose-6-phosphate dehydrogenase (G6PD)-deficient persons, in whom it can cause serious hemolysis; G6PD deficiency must therefore be excluded before primaquine is prescribed. Because of the increasing spread and intensity of antimalarial drug resistance, the Centers for Disease Control and Prevention recommends that travelers and their providers consider their destination, type of travel, and current medications and health risks when choosing antimalarial chemoprophylaxis.

III-259. The answer is C. *(Chap. 220)* The patient has signs and symptoms consistent with an infection with *Babesia microti*. Symptoms typically develop 1–4 weeks after tick bite. Patients experience a gradual onset of fatigue, malaise, and weakness. Fever can reach 40.9°C (105.6°F) and often is accompanied by chills, sweats, headache, myalgia, and anorexia. Less frequent symptoms include arthralgia, nausea, vomiting, and dry cough. Sore throat, photophobia, abdominal pain, weight loss, shortness of breath, neck stiffness, and emotional lability have been reported. On physical examination, fever is the salient feature. Splenomegaly and hepatomegaly occasionally are noted, but lymphadenopathy is absent. Ecchymoses, petechiae, jaundice, slight pharyngeal erythema, and retinopathy with splinter hemorrhages and retinal infarcts rarely are observed. Screening laboratory tests can help support the diagnosis of babesiosis. A complete blood count often shows anemia and thrombocytopenia. White blood cell counts can be elevated, reduced, or unchanged, but neutropenia occurs in approximately three-quarters of infants and one-third of adults. A low haptoglobin level or an elevated lactate dehydrogenase level is consistent with hemolytic anemia. Liver function tests often reveal elevated levels of alkaline phosphatase, aspartate and alanine aminotransferases, and bilirubin. Urinalysis may show hemoglobinuria, excess urobilinogen, and proteinuria. A specific diagnosis usually is established by microscopic examination of Giemsa-stained thin blood smears (Figure III-259). *Babesia* trophozoites appear round or ameboid. The ring form is most common and lacks the central brownish deposit (hemozoin) typical of *Plasmodium falciparum* trophozoites. Other distinguishing features are the absence of schizonts and gametocytes and the occasional presence of tetrads (“Maltese cross”). Tetrads are characteristic of *B. microti*, *B. duncani*, *B. venatorum,* and *B. divergens*–like organisms in human erythrocytes but rarely are observed. Because parasitemia may be as low as 0.01%, particularly at the onset of symptoms, identification of the parasite may require multiple blood smears over several days. Parasitemia generally ranges from 0.1 to 5% but has reached as high as 85% in an immunocompromised patient. If parasites cannot be identified by microscopy and the disease is still suspected, amplification of the *Babesia* 18S rRNA gene by polymerase chain reaction (PCR) or real-time PCR is recommended. Real-time PCR assays detect as few as 0.1–10 parasites per microliter of blood, increasing analytical sensitivity by 10- to 1000-fold over that of blood smear examination.

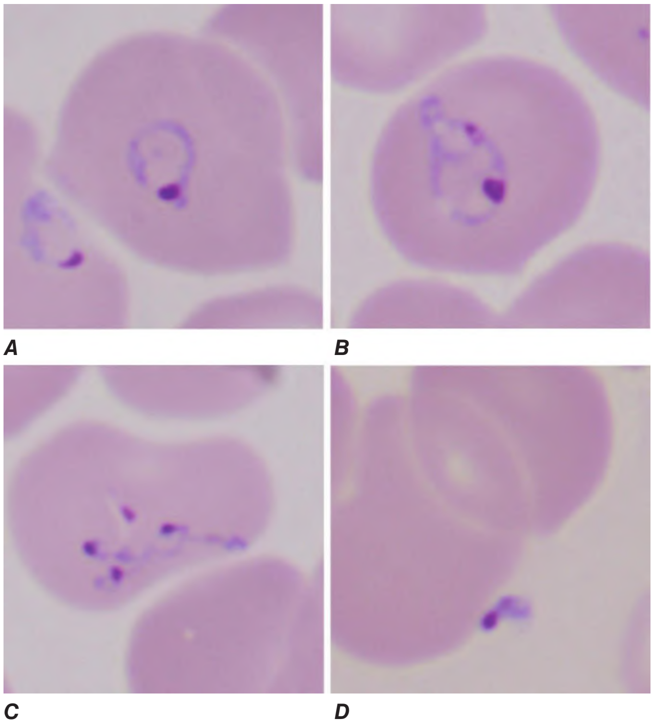


FIGURE III-259 Giemsa-stained thin blood films showing *Babesia microti* parasites. *B. microti* are obligate parasites of erythrocytes. Trophozoites may appear as ring forms (***A***) or as ameboid forms (***B***). Merozoites can be arranged in tetrads that are pathognomonic (***C***). Extracellular parasites can be noted, particularly when parasitemia is high (***D***). (Reproduced with permission from Vannier E, Krause PJ. Human babesiosis. *N Engl J Med* 366:2397, 2012.)

III-260. The answer is C. *(Chap. 221)* Most cases of leishmaniasis occur in the Indian subcontinent and Sudan. Demonstration of amastigotes in smears of tissue aspirates is the gold standard for the diagnosis of visceral leishmaniasis. The sensitivity of splenic smears is >95%, whereas smears of bone marrow (60–85%) and lymph node aspirates (50%) are less sensitive. Culture of tissue aspirates increases sensitivity. Splenic aspiration is invasive and may be dangerous in untrained hands. Several serologic techniques are currently used to detect antibodies to *Leishmania*. An enzyme-linked immunosorbent assay and the indirect immunofluorescent antibody test are used in sophisticated laboratories. In the field, however, a rapid immunochromatographic test based on the detection of antibodies to a recombinant antigen (rK39) consisting of 39 amino acids conserved in the kinesin region of *L. infantum* is used worldwide. The test requires only a drop of finger-prick blood or serum, and the result can be read within 15 minutes. Except in East Africa (where both its sensitivity and its specificity are lower), the sensitivity of the rK39 rapid diagnostic test (RDT) in immunocompetent individuals is ~98% and its specificity is ~90%. In Sudan, an RDT based on a new synthetic polyprotein, rK28, was more sensitive (96.8%) and specific (96.2%) than rK39-based RDTs. Since these antibody detection tests remain positive for years after cure, they cannot be used for measurement of cure or detection of relapse.

III-261. The answer is A. *(Chap. 222)* First described in 1909 by Carlos Chagas, Chagas disease (American trypanosomiasis) is a zoonosis caused by the flagellated protozoan *Trypanosoma cruzi*. *T. cruzi* infection is primarily a zoonosis transmitted to a range of wild and domestic mammals by blood-sucking triatomine bugs. After a frequently asymptomatic acute phase, 30–40% of patients develop life-threatening chronic cardiomyopathy and/or digestive-tract dysfunction over the course of decades. Chagas disease imposes an important human and social burden in Latin America and has recently spread outside its natural boundaries to become a global public health problem. *T. cruzi* can be transmitted congenitally from mother to newborn, by transfusion of blood products, by tissue or organ transplantation, or by ingestion of contaminated food or drink. Congenital infection occurs in 1–10% of newborns of infected mothers. The risk of infection from contaminated blood products is low (1.7% overall, 13% for platelet recipients, and close to 0% for recipients of red blood cells and plasma). Transmission by infected organ and tissue transplants mostly affects heart, liver, and kidney recipients. Oral transmission is increasingly reported after ingestion of contaminated food (berries) or drinks (fruit or sugar cane juice) and occasionally causes outbreaks. An estimated 5.7 million people are infected by *T. cruzi*, including >1 million individuals with chronic cardiomyopathy. The acute phase remains undetected and undiagnosed in most individuals. Deer ticks commonly transmit Lyme disease.

III-262. The answer is D. *(Chap. 222)* This patient most likely has chronic Chagas disease with cardiac involvement and biventricular systolic dysfunction. Chagas disease is a health problem in Latin America. Most acute cases occur in children, but the epidemiology is uncertain since most cases go undiagnosed. The heart is the organ most often involved in chronic Chagas disease with biventricular systolic dysfunction and conduction abnormalities (right bundle branch block and left anterior hemiblock). Apical aneurysms and mural thrombi may occur. Detection of circulating parasites by microscopy of the blood with concentration (e.g., by the Strout method, microhematocrit) or by nucleic acid–based assay (polymerase chain reaction) is the best diagnostic approach when the parasitemia level is high—i.e., during the acute phases, including reactivation. Once parasitemia becomes undetectable by microscopy (a point marking the end of the acute phase), diagnosis relies on immunologic tests that detect anti–*Trypanosoma cruzi* IgG. The most common techniques include a conventional or recombinant enzyme-linked immunosorbent assay and immunofluorescence assays. Two positive serologic tests using different techniques and targeting different antigens confirm the diagnosis of Chagas disease during the chronic phase. In the presence of discordant serologic results, a third serologic test is warranted. Given the patient's demographics, lack of coronary artery disease risk factors, and indolent symptoms, acute myocardial infarction, ischemic cardiomyopathy, and hypertensive cardiomyopathy are less likely diagnoses. Right heart catheterization with placement of a Swan-Ganz catheter could quantify left and right heart pressures and cardiac output but would not be diagnostic.

III-263. The answer is A. *(Chap. 222)* Only two drugs, benznidazole and nifurtimox, have shown efficacy against *Trypanosoma cruzi* infection when administered for ≥30 days. While these drugs have been used since the early 1970s, many questions remain about their mode of action and efficacy at the different stages of infection. The treatment goal depends on the clinical stage; the overall objectives are to cure patients who have recent infection or reactivation, to reduce morbidity, and to prevent transmission at later stages. As benznidazole seems better tolerated than nifurtimox in adults, it is the recommended first-line drug in adults. Close (e.g., weekly) clinical and biological monitoring is necessary during treatment. While treatment is usually prescribed for 60 days, the optimal duration remains a matter of debate, with a growing interest in shorter courses. Treatment should be undertaken for all children, women of childbearing age, patients in the acute phase, and patients with reactivation. A negative pregnancy test is mandatory before initiating treatment as the recommended drugs have not been proven to be safe in pregnancy. The efficacy of second-line treatment (e.g., nifurtimox after failure with benznidazole) has not been evaluated to date.

III-264. The answer is A. *(Chap. 222)* Human African trypanosomiasis (HAT), or sleeping sickness, is caused by the protozoan *Trypanosoma brucei* complex. HAT remains a major public health problem in Africa despite its near-eradication in the 1960s. While HAT only occurs in sub-Saharan Africa, it is important to distinguish between the West African (T b gambiense) and East African (T b rhodesiense) forms. Tsetse flies are the transmission vector for both forms. Humans are the major reservoir of West African trypanosomiasis, and it occurs in rural areas, rarely affecting tourists. Antelope and cattle are the reservoir for T b rhodesiense, and infection has been reported in safari tourists. A primary lesion (trypanosomal chancre) typically appears a week after the bite of an infected tsetse fly. This is followed by a systemic illness with fever and lymphadenopathy (stage 1 disease). Myocarditis may occur, which can be fatal. Central nervous system (CNS) involvement follows (stage 2 disease) with cerebrospinal fluid (CSF) pleocytosis, elevated protein, and elevated pressure. During this stage, trypanosomes may be found in CSF. T b rhodesiense tends to be more aggressive, with CNS disease developing earlier than with T b gambiense. Symptoms during stage 2 disease include progressive somnolence and indifference, sometimes alternating with insomnia and nighttime restlessness. If untreated, symptoms progress to coma and death. Diagnosis requires demonstration of the protozoa from blood, CSF, lymph node material, bone marrow, or chancre fluid. There are serologic tests for T b gambiense, but they lack the sensitivity or specificity for treatment decisions. There are no commercially available polymerase chain reaction tests. All patients with HAT should have a lumbar puncture to evaluate for CNS involvement as that will determine therapy. Suramin is effective for stage 1 East African HAT (T b rhodesiense). Pentamidine is first-line treatment for stage 1 West African HAT. When CSF is involved, eflornithine is used for West African HAT and melarsoprol for East African HAT. Melarsoprol is an arsenical that is highly toxic, with a risk of encephalopathy. HAT poses complex public-health and epizootic problems in Africa. Considerable progress has been made in many areas through control programs that focus on eradication of vectors and drug treatment of infected humans. People can reduce their risk of acquiring trypanosomiasis by avoiding areas known to harbor infected insects, by wearing protective clothing, and by using insect repellent. Chemoprophylaxis is not recommended, and no vaccine is available to prevent transmission of the parasites.

III-265. **The answer is C.** *(Chap. 223)* The MRI shows the classic lesions of encephalitis due to *Toxoplasma gondii* in a patient with advanced immunosuppression due to HIV infection. Cats are the definitive host for the sexual phase of *Toxoplasma*, and oocysts are shed in their feces. In the United States, up to 30% of 19-year-olds and up to 67% of >50-year-olds have serologic evidence of *Toxoplasma* exposure. Patients with HIV infection are at risk of reactivation of latent toxoplasmosis with resultant encephalitis once the CD4 T-cell count falls below 100/μL. Patients receiving immunosuppressive medication for lymphoproliferative disease or solid organ transplant are also at risk for reactivation of latent disease. Although the central nervous system (CNS) is the most common site of symptomatic reactivation disease, the lymph nodes, lung, heart, eyes, and gastrointestinal tract may be involved. *Toxoplasma* usually causes encephalitis not meningitis; therefore, cerebrospinal fluid findings may be unremarkable or have modest elevations of cell count and protein (with normal glucose). The treatment of choice for CNS toxoplasmosis is pyrimethamine plus sulfadiazine. Trimethoprim-sulfamethoxazole is an acceptable alternative. The differential diagnosis of encephalitis in patients with AIDS includes lymphoma, metastatic tumor, brain abscess, progressive multifocal leukoencephalopathy, fungal infection, and mycobacterial infection. In this case, given the classic MRI, toxoplasmosis is the most likely diagnosis.

III-266. **The answer is C.** *(Chap. 224)* The coccidian parasite *Cryptosporidium* causes diarrheal disease that is self-limited in immunocompetent human hosts but can be severe in persons with AIDS or other forms of immunodeficiency. Evaluation starts with fecal examination for small oocysts, which are smaller (4–5 μm in diameter) than the fecal stages of most other parasites. Because conventional stool examination for ova and parasites (O+P) does not detect *Cryptosporidium*, specific testing must be requested. Detection is enhanced by evaluation of stools (obtained on multiple days) by several techniques, including modified acid-fast and direct immunofluorescent stains and enzyme immunoassays. Nitazoxanide, approved by the U.S. Food and Drug Administration for the treatment of cryptosporidiosis, is available in tablet form for adults (500 mg twice daily for 3 days) and as an elixir for children. This agent has not been effective for the treatment of HIV-infected patients, in whom improved immune status due to antiretroviral therapy can lead to amelioration of cryptosporidiosis. Otherwise, treatment includes supportive care with replacement of fluids and electrolytes and administration of antidiarrheal agents.

III-267. **The answer is C.** *(Chap. 224)* Of the listed protozoa, only *Giardia* can be diagnosed with stool ova and parasite examination (Table III-267). Stool antigen immunoassay can be utilized to diagnose *Giardia* and *Cryptosporidium*. Fecal acid-fast testing may be used to diagnose *Cryptosporidium*, *Isospora*, and *Cyclospora*. Microsporidia requires special fecal stains or tissue biopsy for diagnosis.

TABLE III-267 Diagnosis of Intestinal Protozoal Infections

Parasite	Stool O+P[a]	Fecal Acid-Fast Stain	Fecal Antigen Immunoassays	Fecal NAATs[b]	Other
Giardia	+		+	+	
Cryptosporidium	–	+	+	+	
Isospora	–	+		+	
Cyclospora	–	+		+	
Microsporidia	–			+	Special fecal stains, tissue biopsies

[a] O+P, ova and parasites.

[b] NAAT, Nucleic acid amplification test.

III-268. The answer is C. *(Chap. 224) Trichomonas vaginalis*—one of the most prevalent protozoan parasites in the United States—is a pathogen of the genitourinary tract and a major cause of symptomatic vaginitis. Although the organism can survive for a few hours in moist environments and could be acquired by direct contact, person-to-person venereal transmission accounts for virtually all cases of trichomoniasis. Its prevalence is greatest among persons with multiple sexual partners and among those with other sexually transmitted diseases. Many men infected with *T. vaginalis* are asymptomatic, although some develop urethritis and a few have epididymitis or prostatitis. In contrast, infection in women, which has an incubation period of 5–28 days, is usually symptomatic and manifests with malodorous vaginal discharge (often yellow), vulvar erythema and itching, dysuria or urinary frequency (in 30–50% of patients), and dyspareunia. Detection of motile trichomonads by microscopic examination of wet mounts of vaginal or prostatic secretions has been the conventional means of diagnosis. Although this approach provides an immediate diagnosis, its sensitivity for the detection of *T. vaginalis* is only ~50–60% in routine evaluations of vaginal secretions. Direct immunofluorescent antibody staining is more sensitive (70–90%) than wet-mount examinations. *T. vaginalis* can be recovered from the urethra of both males and females and is detectable in males after prostatic massage. Nucleic acid amplification tests are approved by the U.S. Food and Drug Administration and are highly sensitive and specific for urine and for endocervical and vaginal swabs from women. Metronidazole (either a single 2-g dose or 500-mg doses twice daily for 7 days) or tinidazole (a single 2-g dose) is effective. All sexual partners must be treated concurrently to prevent reinfection, especially from asymptomatic males. In males with persistent symptomatic urethritis after therapy for nongonococcal urethritis, metronidazole therapy should be considered for possible trichomoniasis. Alternatives to metronidazole for treatment during pregnancy are not readily available. Reinfection often accounts for apparent treatment failures, but strains of *T. vaginalis* exhibiting high-level resistance to metronidazole have been encountered. Treatment of these resistant infections with higher oral doses, parenteral doses, or concurrent oral and vaginal doses of metronidazole or with tinidazole has been successful.

III-269. The answer is E. *(Chap. 224)* Giardiasis is diagnosed by detection of parasite antigens in the feces or by visualizing cysts or trophozoites in feces or small intestine. There is no reliable serum test for this disease. As a wide variety of pathogens are responsible for diarrheal illness, some degree of diagnostic testing beyond the history and physical examination is required for definitive diagnosis. Colonoscopy does not have a role in diagnosing *Giardia*. Giardiasis can persist in symptomatic patients and should be treated. Severe symptoms such as malabsorption, weight loss, growth retardation, and dehydration may occur in prolonged cases. Additionally, extraintestinal manifestations such as urticarial, anterior uveitis, and arthritis have been associated with potential giardiasis. A single oral 2-g dose of tinidazole is reportedly more effective than a 5-day course of metronidazole, with cure rates of >90% for both. Paromomycin, a poorly absorbed oral aminoglycoside, can be used for symptomatic patients during pregnancy, but its efficacy for eradicating infection is not known. Clindamycin and albendazole do not have a role in treatment of giardiasis. Refractory disease with persistent infection can be treated with a longer duration of metronidazole.

III-270. The answer is A. *(Chap. 226)* Human trichinellosis is often caused by the ingestion of infected pork products and thus can occur in almost any location where the meat of domestic or wild swine is eaten. Human trichinellosis may also be acquired from the meat of other animals, including dogs (in parts of Asia and Africa), horses (in Italy and France), and bears and walruses (in northern regions). Although cattle (being herbivores) are not natural hosts of *Trichinella*, beef has been implicated in outbreaks when contaminated or adulterated with trichinosis-contaminated pork. Laws that prohibit the feeding of uncooked garbage to pigs have greatly reduced the transmission of trichinellosis in the United States. About 12 cases of trichinellosis are reported annually in the United States, but most mild cases probably remain undiagnosed. Recent U.S. and Canadian outbreaks have been attributable to consumption of wild game (especially bear meat) and, less frequently, of pork.

III-271. The answer is E. *(Chap. 226)* Human trichinellosis is often caused by the ingestion of infected pork products and thus can occur in almost any location where the meat of domestic or wild swine is eaten. Recent U.S. and Canadian outbreaks have been attributable to consumption of wild game (especially bear meat) and, less frequently, of pork. Clinical symptoms of trichinellosis arise from the successive phases of parasite enteric invasion, larval migration, and muscle encystment. Most light infections (those with <10 larvae per gram of muscle) are asymptomatic, whereas heavy infections (which can involve >50 larvae per gram of muscle) can be life-threatening. Invasion of the gut by large numbers of parasites occasionally provokes diarrhea during the first week after infection. Abdominal pain, constipation, nausea, or vomiting also may be prominent. Symptoms due to larval migration and muscle invasion begin to appear in the second week after infection. The migrating *Trichinella* larvae provoke a marked local and systemic hypersensitivity reaction, with fever and hypereosinophilia. Periorbital and facial edema is common, as are hemorrhages in the subconjunctivae, retina, and nail beds ("splinter" hemorrhages). A maculopapular rash, headache, cough, dyspnea, or dysphagia sometimes develops. Myocarditis with tachyarrhythmias or heart failure—and, less commonly, encephalitis or pneumonitis—may develop and accounts for most deaths of patients with trichinellosis.

On onset of larval encystment in muscle 2–3 weeks after infection, symptoms of myositis with myalgias, muscle edema, and weakness develop, usually overlapping with the inflammatory reactions to migrating larvae. The most commonly involved muscle groups include the extraocular muscles; the biceps; and the muscles of the jaw, neck, lower back, and diaphragm. Peaking ~3 weeks after infection, symptoms subside only gradually during a prolonged convalescence. Blood eosinophilia develops in >90% of patients with symptomatic trichinellosis and may peak at a level of >50% 2–4 weeks after infection. Serum levels of muscle enzymes, including creatine phosphokinase, are elevated in most symptomatic patients. Most lightly infected patients recover uneventfully with bedrest, antipyretics, and analgesics. Glucocorticoids are beneficial for severe myositis and myocarditis. Mebendazole and albendazole are active against enteric stages of the parasite, but their efficacy against encysted larvae has not been conclusively demonstrated.

III-272 and III-273. The answers are D and B, respectively. *(Chap. 226)* Visceral larva migrans, caused in this case by the canine roundworm *Toxocara canis*, most commonly affects young children who are exposed to canine stool. *Toxocara* eggs are ingested and begin their life cycle in the small intestine. They migrate to many tissues in the body. Particularly characteristic of this illness are hepatosplenomegaly and profound eosinophilia, at times close to 90% of the total WBC count. Staphylococci will not typically cause eosinophilia. Trichinellosis, caused by ingesting meat from carnivorous animals that has been infected with Trichinella cysts, does not cause hepatosplenomegaly and is uncommon without eating a suspicious meal. Giardiasis is characterized by profuse diarrhea and abdominal pain without systemic features or eosinophilia. Cysticercosis typically causes myalgias and can spread to the brain, where it is often asymptomatic but can lead to seizures. The vast majority of *Toxocara* infections are self-limited and resolve without therapy. Rarely, severe symptoms may develop with deaths due to CNS, myocardial, or respiratory disease. Severe myocardial involvement manifests as an acute myocarditis. In these patients, glucocorticoids are administered to reduce the inflammatory complications. Anthelmintic drugs such as albendazole, mebendazole, or praziquantel have not been shown conclusively to alter the course of visceral larval migrans. Metronidazole is used for infections due to Trichomonas, not tissue nematodes.

III-274. The answer is A. *(Chap. 226)* This patient has cutaneous larva migrans. Cutaneous larva migrans ("creeping eruption") is a serpiginous skin eruption caused by burrowing larvae of animal hookworms, usually the dog and cat hookworm *Ancylostoma braziliense*. The larvae hatch from eggs passed in dog and cat feces and mature in the soil. Humans become infected after skin contact with soil in areas frequented by dogs and cats, such as areas underneath house porches. Cutaneous larva migrans is prevalent among children and travelers in regions with warm humid climates, including the southeastern United States. After larvae penetrate the skin, erythematous lesions form along the tortuous tracks of their migration through the dermal-epidermal junction; the larvae advance several centimeters in a day. The intensely pruritic lesions may occur anywhere on the body and can be numerous if the patient has lain on the ground. Vesicles and bullae may form later. The animal hookworm larvae do not mature in humans and, without treatment, will die after an interval ranging from weeks to a couple of months, with resolution of skin lesions. The diagnosis is made on clinical grounds. Skin biopsies only rarely detect diagnostic larvae. Symptoms can be alleviated by ivermectin or albendazole. *Toxocara* causes visceral and ocular larva migrans. *Angiostrongylus cantonensis* (rat lung worm) causes an eosinophilic meningitis. *Wuchereria bancrofti* is one of the causes of filariasis, which is found in the tropics and subtropics. *Schistosoma mansoni* is caused by exposure to freshwater bodies of water and causes intestinal illness.

III-275. The answer is E. (*Chap. 227*, https://www.cdc.gov/parasites/strongyloides/health_professionals/index.html#dx) This patient has hyperinfection syndrome with *Strongyloides*. *S. stercoralis* is spottily distributed in tropical areas and other hot, humid regions and is particularly common in Southeast Asia, sub-Saharan Africa, and Brazil. In the United States, the parasite is endemic in parts of the Southeast and is found in immigrants, refugees, travelers, and military personnel who have lived in endemic areas. In uncomplicated strongyloidiasis, many patients are asymptomatic or have mild cutaneous and/or abdominal symptoms. Recurrent urticaria, often involving the buttocks and wrists, is the most common cutaneous manifestation. Migrating larvae can elicit a pathognomonic serpiginous eruption, *larva currens* ("running larva"). This pruritic, raised, erythematous lesion advances as rapidly as 10 cm/h along the course of larval migration. Adult parasites burrow into the duodenojejunal mucosa and can cause abdominal (usually midepigastric) pain, which resembles peptic ulcer pain except that it is aggravated by food ingestion. Nausea, diarrhea, gastrointestinal bleeding, mild chronic colitis, and weight loss can occur. Small-bowel obstruction may develop with early, heavy infection. Pulmonary symptoms are rare in uncomplicated strongyloidiasis. Eosinophilia is common, with levels fluctuating over time. The ongoing autoinfection cycle of *S. stercoralis* is normally constrained by unknown factors of the host's immune system. Abrogation of host immunity, especially with glucocorticoid therapy and much less commonly with other immunosuppressive medications, leads to hyperinfection, with the generation of large numbers of filariform larvae. Colitis, enteritis, or malabsorption may develop. In disseminated strongyloidiasis, larvae may invade not only gastrointestinal tissues and the lungs but also the central nervous system, peritoneum, liver, and kidneys. Moreover, bacteremia may develop because of the passage of enteric flora through disrupted mucosal barriers. Gram-negative sepsis, pneumonia, or meningitis may complicate or dominate the clinical course. Eosinophilia is often absent in severely infected patients. Disseminated strongyloidiasis, particularly in patients with unsuspected infection who are given glucocorticoids, can be fatal. In disseminated strongyloidiasis, filariform larvae should be sought in stool as well as in samples obtained from sites of potential larval migration, including sputum, bronchoalveolar lavage fluid, or surgical drainage fluid.

III-276. The answer is C. *(Chap. 227) Ascaris* is widely distributed in tropical and subtropical regions as well as in other humid areas in more temperate regions of the world. Transmission typically occurs through fecally contaminated soil and is due either to a lack of sanitary facilities or to the use of human feces as fertilizer. With their propensity for hand-to-mouth fecal carriage, younger children are most often affected. During the lung phase of larval migration, ~9–12 days after egg ingestion, patients may develop an irritating nonproductive cough and burning substernal discomfort that is aggravated by coughing or deep inspiration. Dyspnea and blood-tinged sputum are less common. Fever can occur. Eosinophilia develops during this symptomatic phase and subsides slowly over weeks. The eosinophilia that is prominent during this early stage usually decreases to minimal levels in established infection. Chest x-rays may reveal evidence of eosinophilic pneumonitis (Löffler syndrome) with rounded infiltrates a few millimeters to several centimeters in size. These infiltrates may be transient and intermittent, clearing after several weeks. Where there is seasonal transmission of the parasite, seasonal pneumonitis with eosinophilia may develop in previously infected and sensitized hosts. In established infections, adult worms in the small intestine usually cause no symptoms. In heavy infections, particularly in children, a large bolus of entangled worms can cause pain and small-bowel obstruction, sometimes complicated by perforation, intussusception, or volvulus. Single worms may cause disease when they migrate into aberrant sites. A large worm can enter and occlude the biliary tree, causing biliary colic, cholecystitis, cholangitis, pancreatitis, or (rarely) intrahepatic abscesses.

III-277. The answer is A. *(Chap. 227*) Ascariasis should always be treated, even in asymptomatic cases, to prevent serious intestinal complications. Albendazole, mebendazole, and ivermectin are effective. These agents should not be administered to pregnant women. Pyrantel is safe in pregnancy. Metronidazole is used for anaerobic bacterial and Trichomonas infections. Fluconazole is mostly used to treat *Candida* infections. Diethylcarbamazine is first-line therapy for active lymphatic filariasis.

III-278. The answer is E. *(Chap. 227)* This patient's most likely diagnosis is anisakiasis. This is a nematode infection where humans are an accidental host. It occurs hours to days after ingesting eggs that previously settled into the muscles of fish. The incidence of anisakiasis in the United States has increased as a result of the growing popularity of raw fish dishes. Most cases occur in Japan, the Netherlands, and Chile, where raw fish—sashimi, pickled green herring, and ceviche, respectively—are national culinary staples. Anisakid nematodes parasitize large sea mammals such as whales, dolphins, and seals. As part of a complex parasitic life cycle involving marine food chains, infectious larvae migrate to the musculature of a variety of fish. The main risk factor for infection is eating raw fish. Presentation mimics an acute abdomen. History is critical as upper endoscopy is both diagnostic and curative. The implicated nematodes burrow into the mucosa of the stomach causing intense pain and must be manually removed by endoscope or, on rare occasion, surgery. There is no medical agent known to cure anisakiasis. Anisakid larvae in saltwater fish are killed by cooking to 60°C, freezing at –20°C for 3 days, or commercial blast freezing, but usually not by salting, marinating, or cold smoking.

III-279. The answer is B. *(Chap. 228)* This patient has acute adenolymphangitis (ADL), a presentation of lymphatic filariasis. Lymphatic filariasis is caused by *Wuchereria bancrofti*, *Brugia malayi*, or *B. timori*. *W. bancrofti*, the most widely distributed filarial parasite of humans, affects an estimated 110 million people, and is found throughout the tropics and subtropics, including Asia and the Pacific Islands, Africa, areas of South America, and the Caribbean basin. Humans are the only definitive host for the parasite. Generally, the subperiodic form is found only in the Pacific Islands; elsewhere, *W. bancrofti* is nocturnally periodic. Nocturnally periodic forms of microfilariae are scarce in peripheral blood by day and increase at night, whereas subperiodic forms are present in peripheral blood at all times and reach maximal levels in the afternoon. Natural vectors for *W. bancrofti* are *Culex* mosquitoes in urban settings and *Anopheles* or *Aedes* mosquitoes in rural areas. Brugian filariasis due to *B. malayi* occurs primarily in eastern India, Indonesia, Malaysia, and the Philippines. *B. malayi* also has two forms distinguished by the periodicity of microfilaremia. The more common nocturnal form is transmitted in areas of coastal rice fields, while the subperiodic form is found in forests. *B. malayi* naturally infects cats as well as humans. The distribution of *B. timori* is limited to the islands of southeastern Indonesia. The most common presentations of lymphatic filariasis is asymptomatic (or subclinical) microfilaremia, hydrocele, acute ADL, and chronic lymphatic disease. Although they may be clinically asymptomatic, virtually all persons with *W. bancrofti* or *B. malayi* microfilaria have some degree of subclinical disease that includes microscopic hematuria and/or proteinuria, dilated (and tortuous) lymphatics (visualized by imaging), and—in men with *W. bancrofti* infection—scrotal lymphangiectasia (detectable by ultrasound). ADL is characterized by high fever, lymphatic inflammation (lymphangitis and lymphadenitis), and transient local edema. The lymphangitis is retrograde, extending peripherally from the lymph node draining the area where the adult parasites reside. Regional lymph nodes are often enlarged, and the entire lymphatic channel can become indurated and inflamed. Concomitant local thrombophlebitis can occur as well. The lymphadenitis and lymphangitis can involve both the upper and lower extremities in both bancroftian and brugian filariasis, but involvement of the genital lymphatics occurs almost exclusively with *W. bancrofti* infection. This genital involvement can be manifested by funiculitis, epididymitis, and scrotal pain and tenderness. Microfilariae can be found in blood, in hydrocele fluid, or (occasionally) in other body fluids, but many infected individuals do not have microfilaremia, and definitive diagnosis in such cases can be difficult. Assays for circulating antigens of *W. bancrofti* permit the diagnosis of microfilaremic and cryptic (amicrofilaremic) infection. Two tests are commercially available: an enzyme-linked immunosorbent assay and a rapid-format immunochromatographic card test. Both assays have sensitivities of 93–100% and specificities approaching 100%.

III-280. The answer is B. *(Chap. 228)* Orally administered diethylcarbamazine (DEC; 6 mg/kg daily for 12 days), which has both macro- and microfilaricidal properties, remains the drug of choice for the treatment of active lymphatic filariasis (defined by microfilaremia, antigen positivity, or adult worms on ultrasound), although albendazole (400 mg twice daily by mouth for 21 days) also has demonstrated macrofilaricidal efficacy. A 4- to 6-week course of oral doxycycline (targeting the intracellular *Wolbachia*) also has significant macrofilaricidal activity, as does DEC/albendazole used daily for 7 days. The addition of DEC to a 3-week course of doxycycline is efficacious in lymphatic filariasis.

III-281. The answer is B. *(Chap. 228)* This patient has loiasis caused by the African eye worm Loa. It is endemic to the rain forests of Central and West Africa. Microfilaria circulate periodically in blood with macrofilaria living in subcutaneous tissues including the subconjunctiva. Loiasis is often asymptomatic in indigenous regions with recognition, as in this case, only with visualized macrofilarial migration. Angioedema and swelling may occur in affected areas. Diethylcarbamazine is effective treatment for the macrofilarial and microfilarial stages of disease. Multiple courses may be necessary. Albendazole and ivermectin are effective in reducing microfilarial loads but are not approved by the U.S. Food and Drug Administration for this purpose. There are reports of deaths in patients with heavy loads of microfilaria receiving ivermectin. Terbinafine is the treatment for ringworm. Voriconazole is an antifungal with no activity against worms.

III-282. The answer is A. *(Chap. 229)* Human schistosomiasis is caused by five species of the parasitic genus *Schistosoma*: *S. mansoni, S. japonicum, S. mekongi*, and *S. intercalatum* cause intestinal disease, and *S. haematobium* causes urogenital disease. *Schistosoma* infection is contracted through contact with freshwater bodies harboring infected intermediate-host snails. Cercariae, the infective larval stage released from the snail, penetrate intact human skin within a few minutes after attaching to the skin. The schistosome egg, not the worm, is the only stage of the parasites' life cycle that can be detected in humans, either in excreta or in tissue biopsies. The eggs are large and can easily be distinguished morphologically from other helminth eggs (Figure III-282). *S. haematobium* eggs are ~140 µm long, with a terminal spine; *S. mansoni* eggs are ~150 µm long, with a lateral spine; and *S. japonicum* eggs are smaller, rounder, and ~90 µm long, with a small lateral spine or knob. Cercarial invasion may be associated with dermatitis arising from dermal and subdermal inflammatory reactions in response to dying cercariae that trigger innate immune responses. However, most manifestations of schistosomiasis—in the acute, established, and chronic phases of infection—are due to immunologic reactions to eggs retained in host tissues.

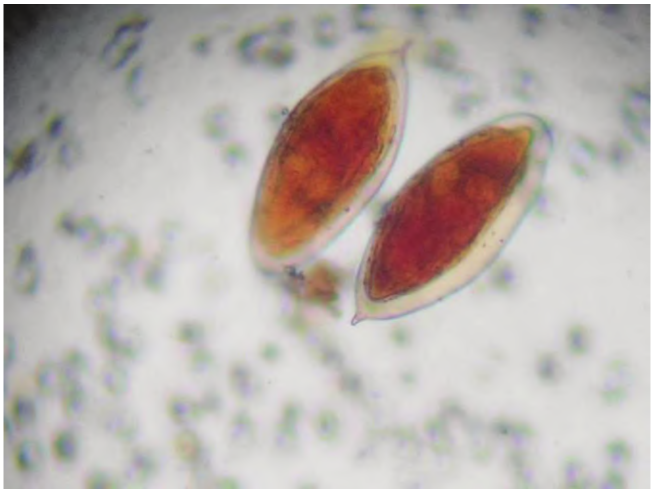


FIGURE III-282

All evidence suggests that schistosome eggs, and not adult worms, induce the organ-specific morbidity caused by schistosome infections.

III-283. **The answer is D.** *(Chap 229)* This patient has Katayama fever caused by infection with *Schistosoma mansoni*. Approximately 4–8 weeks after exposure the parasite migrates through the portal and pulmonary circulations. This phase of the illness may be asymptomatic but, in some cases, evokes a hypersensitivity response and a serum sickness–type illness. Eosinophilia is usual. Since there is not a large enteric burden of parasites during this phase of the illness, stool studies may not be positive and serology may be helpful, particularly in patients from nonendemic areas. Praziquantel is the treatment of choice because Katayama fever may progress to include neurologic complications. Praziquantel remains the treatment for most helminthic infections, including schistosomiasis. Chloroquine is used for treatment of malaria; mebendazole for ascariasis, hookworm, trichinosis, and visceral larval migrans; metronidazole for amebiasis, giardiasis, and trichomoniasis; and thiabendazole for *Strongyloides*.

III-284. **The answer is B.** *(Chap. 229) Schistosoma mansoni* infection of the liver causes cirrhosis from vascular obstruction resulting from periportal fibrosis but relatively little hepatocellular injury. Hepatosplenomegaly, hypersplenism, and esophageal varices develop quite commonly, and schistosomiasis is usually associated with eosinophilia. Spider nevi, gynecomastia, jaundice, and ascites are observed less commonly than they are in alcoholic and postnecrotic fibrosis.

III-285. **The answer is A.** *(Chap. 230)* This patient has neurocysticercosis caused by Taenia solium, as evidenced by her typical CT imaging in someone with the appropriate epidemiologic history and negative HIV testing. The axial CT image demonstrates a parenchymal cysticercus, with enhancement of the cyst wall and an internal scolex (Figure III-285, arrow). The coronal view of the CT demonstrates multiple cysticerci, including calcified lesions from prior infection (arrowheads), viable cysticerci in the basilar cisterns (white arrow), and a large degenerating cysticercus in the Sylvian fissure (black arrow). *T. solium* is found worldwide in areas where pigs are raised and have access to human feces. However, it is most prevalent in Latin America, sub-Saharan Africa, China, India, and Southeast Asia. Cysticerci can be found anywhere in the body but are most commonly detected in the brain, cerebrospinal fluid (CSF), skeletal muscle, subcutaneous tissue, or eye. The clinical presentation of cysticercosis depends on the number and location of cysticerci as well as on the extent of associated inflammatory responses or scarring. Neurologic manifestations are the most common. Seizures are associated with inflammation surrounding cysticerci in the brain parenchyma. These seizures may be generalized, focal, or Jacksonian. Hydrocephalus results from CSF flow obstruction by cysticerci and accompanying inflammation or by CSF outflow obstruction from arachnoiditis. Symptoms of increased intracranial pressure, including headache, nausea, vomiting, changes in vision, dizziness, ataxia, or confusion, are often evident. Patients with hydrocephalus may develop papilledema or display altered mental status. The initial management of neurocysticercosis should focus on symptom-based treatment of seizures or hydrocephalus. Seizures can usually be controlled with antiepileptic treatment. For the treatment of patients with brain parenchymal cysticerci, most authorities favor antiparasitic drugs, including albendazole (15 mg/kg per day for 8–28 days) or praziquantel (50–100 mg/kg daily in three divided doses for 15–30 days). A combination of albendazole and praziquantel (50 mg/kg per day) is more effective in patients with more than two cystic lesions. A longer course or combination therapy is often needed in patients with multiple subarachnoid cysticerci. Both agents may exacerbate the inflammatory response around the dying parasite, exacerbating seizures or hydrocephalus as well. Thus, patients receiving these drugs should be carefully monitored. High-dose glucocorticoids should be used during treatment. Because glucocorticoids induce first-pass metabolism of praziquantel and may decrease its antiparasitic effect, cimetidine should be co-administered to inhibit praziquantel metabolism.

III-286. The answer is B. *(Chap. 230)* The ultrasound demonstrates cystic hydatid disease due to echinococcosis with a visible cyst wall and internal septation. Echinococcosis is usually caused by infection of *Echinococcus granulosus* complex or *E. multilocularis* transmitted to humans via dog feces. *E. granulosus* is found on all continents with high prevalence in China, Central Asia, the Middle East, the Mediterranean region, eastern Africa, and parts of South America. *E. multilocularis*, which causes multiloculated invasive lung lesions, is found in Alpine, sub-Arctic, or Arctic regions including Canada, the United States, China, Europe, and Central Asia. Echinococcal cysts, most commonly in the liver followed by lungs, are typically slowly enlarging and cause symptoms due to space-occupying effects. Cysts are often incidentally discovered on radiologic studies. Compression or leakage into the biliary system may cause symptoms typical for cholelithiasis or cholecystitis. Echinococcal cysts may be characterized by ultrasound. Demonstration of daughter cysts within a larger cyst is pathognomonic. Serodiagnosis may be helpful in questionable cases for diagnosis of *E. granulosus*. Patients with liver cysts typically have positive serology in >90% (but not 100%) of cases. Up to 50% of patients with lung cysts may be seronegative. Biopsy is generally not recommended for cysts close to the liver edge due to the risk of leakage. Small cysts may respond to medical therapy with albendazole or praziquantel. Percutaneous aspiration, infusion of scolicidal agent, and re-aspiration (PAIR) therapy is recommended for most noncomplex, nonsuperficial cysts. Surgical resection is recommended for complex cysts, superficial cysts with risk of leakage, or cysts involving the biliary system. Albendazole therapy is generally administered before and after PAIR or surgical therapy.

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SECTION IV

Disorders of the Cardiovascular System

QUESTIONS

DIRECTIONS: Choose the one best response to each question

IV-1. In the United States, which of the following is the most common cause of death?

A. Accidents and trauma
B. Cancer
C. Cardiovascular diseases
D. Chronic kidney disease
E. Dementia

IV-2. Regarding the associations of gender and cardiovascular disease, which of the following statements is true?

A. Cardiovascular disease accounts for a higher percentage of deaths among men versus women.
B. Exercise electrocardiography has a higher diagnostic accuracy in women than in men for the prediction of epicardial obstructive coronary disease.
C. Obesity and the metabolic syndrome play a less prominent role in the development of coronary atherosclerosis in women than in men.
D. The absolute number of deaths attributable to cardiovascular disease has risen in women over the past several decades.
E. None of the above are true.

IV-3. You are seeing patient RJT, a 45-year-old previously healthy man, for a physical examination. This is his first time coming to a doctor for over 20 years. On examination, you auscultate a grade II diastolic murmur. He is asymptomatic, denying chest pain, dyspnea, edema, or any syncopal or pre-syncopal episodes. Examination reveals no other abnormalities, including normal carotid pulses, a nondisplaced point of maximal impulse on cardiac palpation, and clear lung fields. Electrocardiogram and chest x-ray are normal. What is the next best step for evaluation of his murmur?

A. Cardiac computed tomography
B. Cardiac MRI
C. Carotid ultrasound
D. Echocardiogram
E. No further workup required

IV-4. During myocardial contraction, which of the following biochemical events occur?

A. Adjacent Z lines move closer together
B. A band shortens
C. I band remains constant
D. Thick filament shortens
E. Thin filament shortens

IV-5. You are seeing a 65-year-old man with a history of progressive systolic heart failure and hypotension in the cardiac care unit. Echocardiogram shows a severe reduction in left ventricular function and you clinically make the diagnosis of cardiogenic shock. You wish to start a medication that will increase the inotropic state of his heart. Which intracellular ion will increase as a result of this medication and will be responsible for increasing myocardial contractility (inotropy)?

A. Calcium
B. Chloride
C. Phosphorus
D. Potassium
E. Sodium

IV-6. You are appointed as a cardiac epidemiologist advisor on an international committee setting global health policy. Your committee is assigned to predict health trends in a nation just moving from the first classic stage in the epidemiologic transition ("pestilence and famine") to the second classic stage ("receding pandemics"). In regards to the anticipated patterns of cardiovascular disease (CVD) in this nation, which of the following is true?

A. As this nation enters the stage of receding pandemics, you would expect the majority of cardiovascular disease morbidity and mortality to be due to cardiomyopathies secondary to infectious agents.
B. Each nation or geographical location progresses through the five stages of epidemiologic transition identically in regards to cardiovascular disease risk.
C. In this nation, when CVD mortality peaks, you would expect stroke mortality be outnumbered by coronary heart disease mortality.
D. One would expect a very homogeneous epidemiologic pattern of cardiovascular risk throughout this nation over time.
E. You anticipate that CVD mortality will inexorably climb as this nation progresses through the five stages of the epidemiologic transition.

IV-7. You are working in a rural health clinic in northern India. You evaluate an 8-year-old boy who has never seen a physician. His mother tells you that he is unable to keep up with his peers in terms of physical activity. On your initial examination of his skin, you notice the clubbing and cyanosis in his feet, but his hands appear normal. Without any further examination, you suspect that he has which of the following congenital abnormalities:

A. Atrial septal defect
B. D-transposition of the great arteries
C. Patent ductus arteriosus with secondary pulmonary hypertension
D. Tetralogy of Fallot
E. Ventricular septal defect

IV-8. You are evaluating Mr. Estebez, a 67-year-old owner of a wildly successful chain of sushi restaurants. He complains of shortness of breath with exertion, lower extremity edema, and awakening at night feeling acutely short of breath. You wish to assess his volume status, and know that jugular venous pulse (JVP) assessment is the single most important bedside measurement to aid in this. Regarding JVP measurement, which of the following is true?

A. Measurement of the elevation of the top of the jugular venous pulsation and the sternal inflection point (angle of Louis) will provide a highly accurate measurement of central venous pressure.
B. If done properly, the angle of inclination matters little to the measurement of JVP.
C. In normal patients, the JVP rises with inspiration due to the augmented volume loading of the right heart.
D. The external jugular is preferred over the internal jugular vein due to its ease of visibility.
E. Venous pulsations above the clavicle in the sitting position are abnormal.

IV-9. Which of the following statements is true regarding blood pressure measurements?

A. Systolic pressure increases and diastolic pressure decreases when measured in more distal arteries.
B. Systolic leg blood pressures are usually as much as 20 mmHg lower than arm blood pressures.
C. The difference in blood pressure measured in both arms should be less than 20 mmHg.
D. The concept of "white coat hypertension" (blood pressures measured in office or hospital settings significantly higher than in nonclinical settings) has been shown to be a myth.
E. Using a blood pressure cuff that is too small will result in a marked underestimation of the true blood pressure.

IV-10. Mr. Kobishigawa is a 75-year-old man who presents to your emergency department appearing quite ill. His family says he has not had his normal energy for the last 6 months, and they noted he appeared confused and lethargic for the last day or two. As you take a history from the family, you palpate the patient's radial pulse and notice a regular beat-to-beat variability of pulse amplitude although his rhythm is regular. Indeed, as you later take his blood pressure, you note that only every other phase I (systolic) Korotkoff sound is audible as the cuff pressure is slowly lowered, and that this is independent of the respiratory cycle. Based on this, you suspect Mr. Kobishigawa has which of the following?

A. Cardiac tamponade
B. Pulmonary embolism
C. Atrial fibrillation
D. Constrictive pericarditis
E. Severe left ventricular dysfunction

IV-11. You are evaluating a 42-year-old man with a history of syncope. You auscultate a systolic, crescendo-decrescendo murmur at the lower left sternal border. Which physical examination maneuver and finding is most consistent with hypertrophic obstructive cardiomyopathy versus aortic stenosis?

A. Augmentation of murmur intensity with Valsalva maneuver
B. Augmentation in murmur intensity with passive leg raise
C. Augmentation in murmur intensity with squatting
D. Augmentation in murmur intensity with hand squeeze
E. Reduction in murmur intensity with Valsalva maneuver

IV-12. Which of the following statements regarding normal depolarization patterns of the heart is true?

A. Each normal sinus beat is initiated by spontaneous depolarization in the atrioventricular (AV) node.
B. The normal order of depolarization is sinoatrial node (SA), atrial myocardium, AV node, His bundle, Purkinje fibers, and ventricular myocardium.
C. The right bundle branch bifurcates into an anterior and posterior fascicle.
D. The SA node is unique in its ability to spontaneously depolarize, a quality known as automaticity.
E. Within the ventricular myocardium, depolarization sweeps from epicardium to endocardium.

IV-13. All of the following electrocardiograph waveforms are matched correctly to the cardiac cycle that it represents EXCEPT:

A. P wave—atrial repolarization
B. PR interval—atrial repolarization
C. QRS complex—ventricular depolarization
D. T wave—ventricular repolarization
E. U wave—ventricular repolarization

IV-14. Which of the following mean QRS vectors in the frontal electrocardiographic plane is matched appropriately to its designation?

A. –20°—normal axis.
B. –35°—right axis deviation.
C. 110°—left axis deviation.
D. –80°—extreme axis deviation.
E. All of the above are incorrect.

IV-15. A 58-year-old man presents to the emergency department with crushing substernal chest pain. You suspect myocardial ischemia based on the history. Which of the following is true regarding the electrocardiogram in myocardial ischemia?

A. In acute transmural myocardial ischemia, Q waves typically precede ST-segment elevation by 4–6 hours.
B. ST-segment elevation is less helpful in localizing myocardial ischemia to anatomic areas of the heart than ST depression.
C. Subendocardial ischemia alone results in ST-segment elevation in the leads corresponding to the anatomic area of ischemia.
D. Transmural posterior wall ischemia can result in ST depressions in leads V_1–V_3.
E. Transmural ST-segment elevation in leads II, III, and aVF indicate acute transmural ischemia in the anterior wall.

IV-16. Patient MC is a 77-year-old woman with end-stage renal disease on hemodialysis Monday, Wednesday, and Friday. She presents to the emergency room with dyspnea and fatigue Wednesday morning after missing her Friday and Monday dialysis sessions due to car trouble. An electrolyte abnormality is present. Initial electrocardiogram (ECG) abnormalities are shown in Figure IV-16A under "Mild-Moderate." As the electrolyte abnormality worsens, her ECG progresses as noted under "Moderate-Severe" and finally to the changes noted under "Very Severe." Which electrolyte abnormality is responsible for these increasingly dire ECG abnormalities?

A. Hypercalcemia
B. Hyperkalemia
C. Hypokalemia
D. Hypocalcemia
E. Hyponatremia

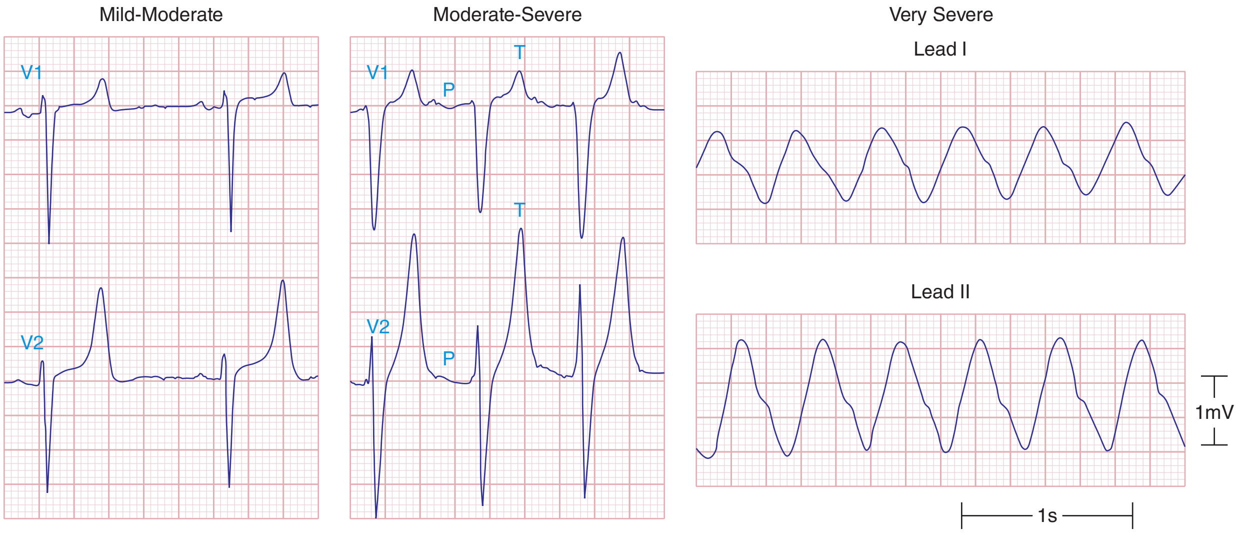


FIGURE IV-16A

IV-17. You are working in the emergency department when patient MM presents in *extremis*. She is a 65-year-old woman with a history of recently diagnosed lymphoma who has not started treatment or undergone staging yet. On presentation, she is markedly diaphoretic and dyspneic. Blood pressure is 70/palp, heart rate is 110 beats/min, and her radial pulse becomes difficult to palpate on inspiration. Electrocardiogram is emergently obtained and shown in Figure IV-17. You note odd changing QRS morphology in leads V_3 and V_4 especially (arrows). What pathology is present and accountable for her shock state?

A. Acute anterior myocardial infarction
B. Chronic obstructive pulmonary disease exacerbation
C. Myocardial amyloidosis
D. Pericardial effusion with tamponade
E. Pulmonary embolism

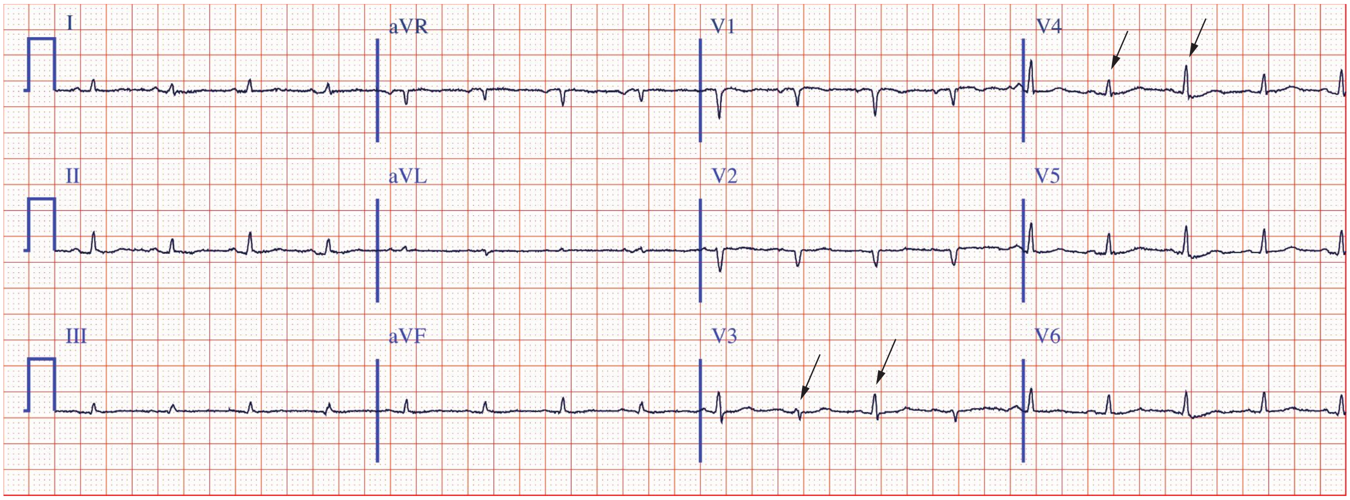


FIGURE IV-17 Adapted with permission from LA Nathanson et al: ECG Wave-Maven. http://ecg.bidmc.harvard.edu.

IV-18. You are seeing Mr. Bilious in the urgent care clinic. He is a 53-year-old man complaining of occasional, pressure-like chest discomfort. The discomfort seems to worsen when he exerts himself, and he has to stop when climbing stairs to allow it to dissipate. You suspect coronary artery disease, and he is not amenable to any invasive testing such as coronary angiography. Which noninvasive test given here has the highest sensitivity currently for detecting >50–70% stenosis in major coronary arteries?

A. Cardiac magnetic resonance perfusion scan
B. Coronary CT angiography
C. Dobutamine echocardiography
D. Exercise echocardiography
E. Single-photon emission computed tomography myocardial perfusion imaging

IV-19. Mr. Tedkia presents to the emergency department with several days of on-and-off chest pressure. Suspecting myocardial ischemia due to coronary artery disease, you refer him for stress and rest rubidium-82 myocardial perfusion positron emission tomography. The results are shown in Figure IV-19A with abnormalities noted by the arrows.

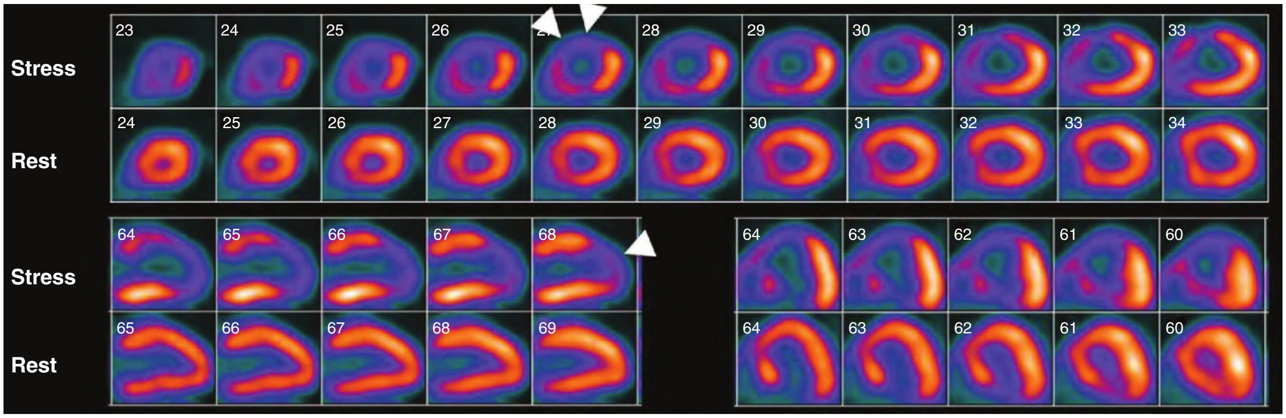


FIGURE IV-19A

This is most indicative of stenosis in which of the following coronary arteries?

A. Left anterior descending artery
B. Left main coronary artery
C. Left circumflex artery
D. Right coronary artery
E. Posterior descending artery

IV-20. You are a cardiologist working today in the cardiac catheterization laboratory. You are performing a right heart catheterization to evaluate a patient for dyspnea. After inserting the catheter into the right internal jugular vein, you advance it and get the subsequent pressure tracings, labeled in Figure IV-20A. Which letter label is incorrectly assigned to its corresponding chamber?

A. A = right atrium.
B. B = right ventricle.
C. C = pulmonary artery.
D. D = pulmonary capillary wedge position.
E. All of the above labels are correctly assigned.

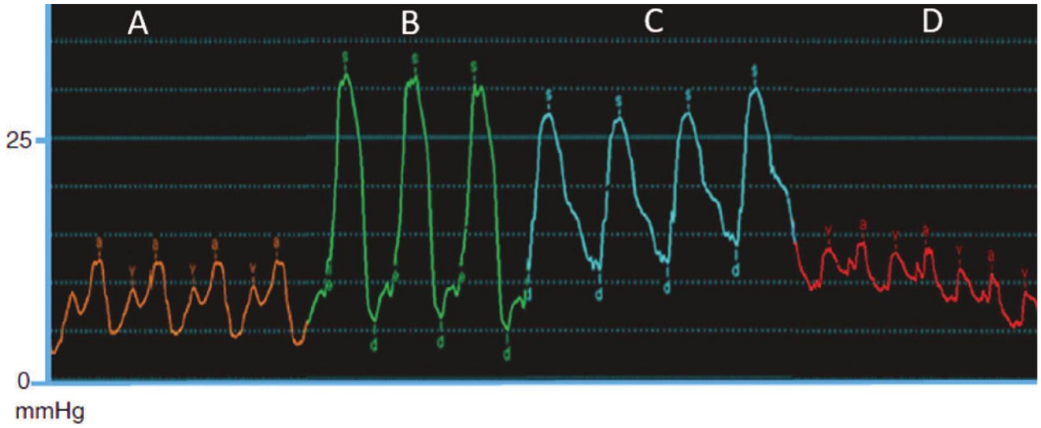


FIGURE IV-20A

IV-21. You are performing a right heart catheterization in a 45-year-old man with suspected pulmonary hypertension. You do indeed note elevated pulmonary arterial pressures, with a mean pulmonary arterial pressure of 45 mmHg. The patient is not hypoxemic. However, you also note the following oxygen saturations from each cardiac chamber:

Superior vena cava—61%
Inferior vena cava—65%
Right atrium—85%
Right ventricle—84%
Pulmonary artery—84%

You suspect which of the following based on this data?

A. Atrial septal defect with left-to-right shunting
B. Aorta to inferior vena cava arteriovenous shunt
C. Patent ductus arteriosus
D. Ventricular septal defect with left-to-right shunting
E. Ventricular septal defect with right-to-left shunting

IV-22. In the normal heart, which of the following represents the only electrical connection between the atria and ventricles?

A. Atrioventricular node
B. Bundle of Kent
C. Purkinje fibers
D. Sinoatrial node
E. None of the above

IV-23. Which of the following is the most common mechanism of cardiac arrhythmia?

A. Decreased cellular coupling
B. Delayed after depolarizations
C. Enhanced automaticity
D. Early after depolarizations
E. Reentry

IV-24. The sinoatrial (SA) node serves as the dominant pacemaker of the heart in normal sinus rhythm. What property of SA nodal cells allows it to act as the primary pacemaker?

A. Location near the superior, lateral area of the right atrium.
B. More numerous intercalated discs of any other myocardial tissue.
C. Most rapid phase 0 depolarization.
D. SA nodal cells are the only cells with the ability to spontaneously depolarize.
E. Spontaneous depolarization during phase 4 of the action potential at a more rapid rate than any other myocardial cells.

IV-25. Mr. Hendricks is a 21-year-old sommelier at a well-known restaurant in the city. His primary hobby is competitive bicycle racing and he has a 150-km race coming up next weekend for which he has been training for the last 6 months. The race coordinators require every competitor to complete a comprehensive cardiovascular assessment prior to competing; thus, he comes to visit your clinic. On your assessment, you note a resting heart rate or 45 beats/min with an occasional pause of up to 2 seconds, particularly during expiration. His blood pressure is 108/72. He feels well and reports no syncopal or presyncopal episodes at rest or during exercise. Aside from the bradycardia, you note no other abnormalities on his examination. His electrocardiogram (ECG) shows sinus rhythm with a PR interval of 128 ms, QRS duration of 80 ms, and occasional pauses as long as 2.2 seconds. Which of the following would be appropriate advice for Mr. Hendricks?

A. Electrophysiologic evaluation for consideration of a pacemaker.
B. He should not compete in the upcoming race due to concern for bradycardia and will need a tilt-table test.
C. No further follow-up is needed. Good luck with the race!
D. Obtain a 48-hour Holter monitor tracing.
E. Undergo a treadmill stress ECG to determine the presence of chronotropic competence.

IV-26. All of the following are reversible causes of sinoatrial node dysfunction EXCEPT:

A. Hypothermia
B. Hypothyroidism
C. Increased intracranial pressure
D. Lithium toxicity
E. Radiation therapy

IV-27. Mr. Judge is a 72-year-old non-smoker who until recently was an avid gardener. However, over the last year, he has noticed increased fatigue while gardening and exerting himself. Physical examination and resting vital signs are normal. Chest x-ray, laboratory studies, and baseline electrocardiogram (ECG) are normal as well. Echocardiogram shows normal biventricular systolic and diastolic function, normal atrial size, and no valvular abnormalities. On an exercise ECG test, his peak heart rate is 96 beats/min and there are no ST-segment alterations. Based on the above data, you suspect his symptoms are due to which of the following?

A. Chronotropic incompetence
B. Heart failure with preserved ejection fraction
C. Lung disease
D. Normal aging
E. Psychosomatic complaints

IV-28. Mr. Vanbakel is an 80-year-old man with a history of hypertension treated with hydrochlorothiazide and metoprolol tartrate. He presents to your clinic with a complaint of fatigue over the past few weeks. On examination, the only notable finding is a heart rate of 40 beats/min. Electrocardiogram (ECG) shows sinus bradycardia with normal PR interval. Laboratory studies show no abnormalities including normal thyroid studies and hemoglobin. The next most reasonable step would be which of the following?

A. Dual-chamber pacemaker implantation
B. Exercise ECG test
C. Start theophylline 100 mg daily
D. Stop metoprolol tartrate
E. Stop hydrochlorothiazide

IV-29. Normal cells within the atrioventricular (AV) node exhibit a property known as decremental conduction. If you wanted to demonstrate this property during an electrophysiology study, which maneuver could you perform?

A. Pace the right atrium at serially more rapid rates and measure the pace-to-His bundle conduction time.
B. Pace the ventricle and record right atrial potentials.
C. Administer atropine 0.04 mg/kg and record AV nodal conduction time by measuring the time it takes an atrial pacing beat to reach the His bundle.
D. Administer metoprolol 10 mg IV and record AV nodal conduction time by measuring the time it takes an atrial pacing beat to reach the His bundle.
E. Administer adenosine 12 mg IV and record the AV nodal recovery time.

IV-30. Mr. Shah is an 87-year-old man with a history of well-treated hypertension and aortic stenosis. Over the last year he became symptomatic from his aortic stenosis. Yesterday, he underwent surgical aortic valve replacement with a bioprosthetic 25-mm valve with excellent intraoperative results. He was rapidly weaned from cardiopulmonary bypass and extubated within 24 hours. Per surgical protocol, he had temporary epicardial pacing wires placed on the ventricular surface and has been pacing at 90 beats/min. On rounds this morning, you briefly pause his ventricular pacing to check his underlying rhythm. You note an atrial rate of 80 beats/min, but a ventricular rate of 32 beats/min with a wide complex QRS. There is no relationship between the P waves and QRS complexes. This patient's bradycardia is most likely due to which of the following?

A. Slowed atrioventricular (AV) nodal recovery after overdrive pacing
B. Endocarditis of the new aortic bioprosthesis causing AV node block
C. Sinoatrial node disease
D. Surgical injury to the AV node
E. Development of a systemic disease such as sarcoidosis or Lyme disease causing AV node dysfunction

IV-31. Mrs. Hellwig is a 25-year-old woman with systemic lupus erythematosus (SLE) complicated by nephropathy, hemolytic anemia, and pleuritis. Her disease is well-controlled on therapy. She recently discovered that she is pregnant and presents today for prenatal counseling. She specifically is concerned about the effect her disease may have on the infant. You tell her that the most common cardiac complication in children born to mothers with SLE is:

A. Sterile, Libman-Sacks endocarditis
B. Dilated cardiomyopathy
C. Atrioventricular block
D. Coronary artery disease
E. Pulmonary hypertension with right ventricular failure

IV-32. You are evaluating Mr. Aggarwal, an 85-year-old man, for fatigue. On examination, he is bradycardic and has occasional cannonball venous pulses in his neck. Electrocardiogram demonstrates complete heart block. All of the following diseases are associated with the development of cardiac conduction disease EXCEPT:

A. Chagas disease
B. Hyperthyroidism
C. Lyme disease
D. Syphilis
E. Systemic lupus erythematosus

IV-33. You are seeing Mr. Johnson who is a 24-year-old previously healthy marathon runner. He is in for his employer-required physical examination. Which of the following rhythms is demonstrated in Figure IV-33?

A. First-degree heart block
B. Mobitz type I, second-degree heart block
C. Mobitz type II, second-degree heart block
D. Normal sinus rhythm
E. Type III heart block

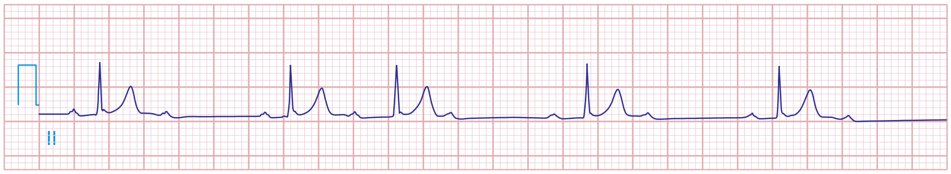


FIGURE IV-33

IV-34. A 47-year-old woman with a history of tobacco abuse and ulcerative colitis is evaluated for intermittent palpitations. She reports that for the last 6 months every 2–4 days she notes a sensation of her heart "flip-flopping" in her chest for approximately 5 minutes. She has not noted any precipitating factors and has not felt light-headed or had chest pains with these episodes. Her physical examination is normal. A resting electrocardiogram reveals sinus rhythm and no abnormalities. Aside from checking serum electrolytes, which of the following is the most appropriate testing?

A. Abdominal CT with oral and IV contrast
B. Event monitor
C. Holter monitor
D. Reassurance with no further testing needed
E. Referral for an electrophysiological study

IV-35. After further testing, the patient is found to have several episodes of atrial premature contractions. Which of the following statements regarding the dysrhythmia in this patient is true?

A. Atrial premature contractions are less common than ventricular premature contractions on extended electrocardiographic monitoring.
B. Echocardiography is indicated to determine whether structural heart disease is present.
C. Metoprolol should be initiated for symptom control.
D. The patient should be reassured that this is not a dangerous condition and does not require further evaluation.
E. The patient should undergo stress test to determine whether ischemia is present.

IV-36. Ms. Milsap is an 18-year-old high school volleyball star with a sports scholarship to the local university. As part of her admission process, she is required to undergo a full medical assessment prior to taking part in collegiate sports. Physical examination reveals no abnormalities, although she reports the rare episode of palpitations and light-headedness. Electrocardiogram reveals a PR interval of 0.06 ms and QRS duration of 140 ms, and a slurred upstroke or delta wave in the initial part of the QRS. You correctly diagnose this as Wolff-Parkinson-White pattern. Which of the following findings is reassuring that Ms. Milsap will suffer no ill effects or need catheter ablation due to this abnormality?

A. Ability to increase the heart rate to 185 beats/min on an exercise treadmill test
B. Electrophysiology study demonstrating that the accessory pathway has both antegrade and retrograde conduction properties
C. Electrophysiology study demonstrating that the accessory pathway is located in the posteroseptal region
D. Exercise treadmill study demonstrating disappearance of the delta wave and wide QRS at a heart rate of 120 beats/min
E. Holter monitoring demonstrating occasional runs of atrial fibrillation

IV-37. A 79-year-old man with a history of coronary artery disease, ischemic cardiomyopathy with a left ventricular ejection fraction of 30%, and hypertension presents to your office with no new complaints. Blood pressure is 108/56, heart rate is irregular at 88 beats/min, and arterial oxygen saturation is 98%. His rhythm strip is shown in Figure IV-37. At his last clinic visit 6 months ago his heart rate was regular and electrocardiogram (ECG) showed no abnormalities. Based on this ECG, the patient now has a definite (class I) indication for which of the following therapies:

A. Amiodarone 400 mg daily
B. Aspirin 325 mg daily
C. Flecainide 600 mg PRN palpitations
D. Systemic anticoagulation with warfarin or a novel oral anticoagulant
E. Transesophageal echocardiography followed by direct current cardioversion

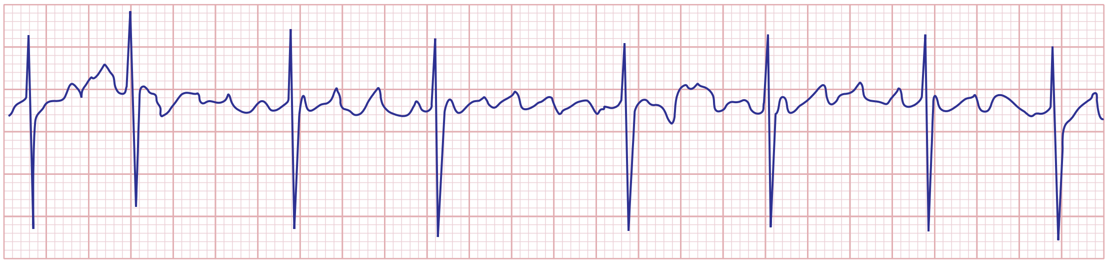


FIGURE IV-37

IV-38. A 76-year-old woman with a history of hypertension, chronic obstructive pulmonary disease, diabetes mellitus, and osteoporosis presents to the emergency department after a fall at home followed immediately by intense left hip pain. She was found by a neighbor after several hours. The patient cannot remember if she lost consciousness. She is exquisitely tender to palpation over the left hip, and her leg is shortened and externally rotated. Her mucous membranes are dry and her skin tents easily. Blood pressure is 170/80 and her heart rate is 130 beats/min. She is dyspneic and wheezing. Her rhythm strip demonstrates an irregular tachycardia, with P waves of at least three different morphologies present. What is the most appropriate first step for her tachycardia?

A. Adenosine 6 mg IV
B. Direct current cardioversion
C. Digoxin 250 mcg IV
D. Metoprolol 5 mg IV
E. Pain control and IV hydration

IV-39. You are working in the emergency department when Mrs. Ramu, a 29-year-old previously healthy woman, presents with palpitations and feeling "odd." On examination, she is not in distress. Blood pressure is 112/87 and heart rate is 160 beats/min. Other than the tachycardia, her physical examination is normal. Electrocardiogram is demonstrated in Figure IV-39. You note unusual deflections in the ST segment marked by the arrows.

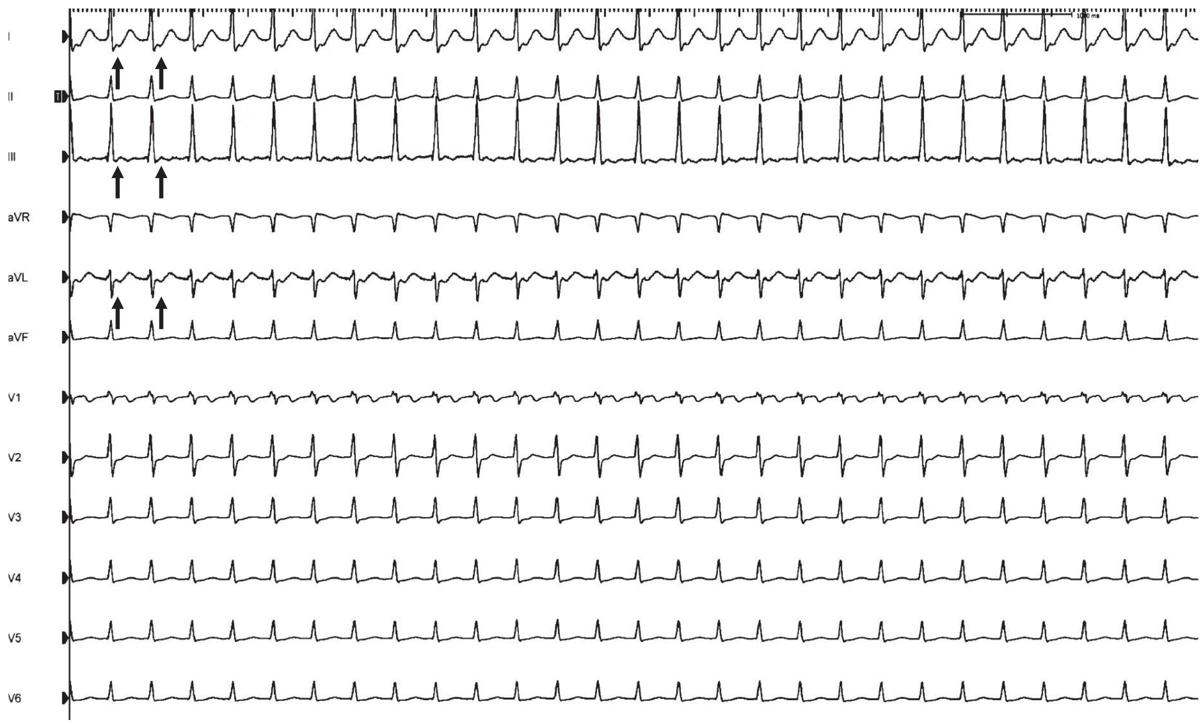


FIGURE IV-39A

You ask her to perform a Valsalva maneuver and her heart rate suddenly drops to 80 beats/min and she quickly feels better. Which rhythm (Figure IV-39A) was her most likely presenting rhythm?

A. Atrial fibrillation
B. Atrial flutter
C. Multifocal atrial tachycardia
D. Orthodromic atrioventricular reentry tachycardia
E. Sinus tachycardia

IV-40. You are the cardiology consultant overnight for a tertiary care medical center. You are paged to the bedside of a 42-year-old man for assessment of tachycardia. He was previously diagnosed with metastatic colon cancer and presents with dyspnea. He has no history of brain metastases, liver failure, or renal failure. On examination, he is tachypneic with a respiratory rate of 20 breaths/min and systemic oxygen saturation is 90% on 4 L nasal cannula oxygen. His heart rate is 120 beats/min and his blood pressure is 110/70. His jugular vein is moderately distended and lung fields are clear. Electrocardiogram shows a P wave before every QRS complex and a QRS complex after every P wave. P wave axis is 40 degrees in the frontal plane. PR interval is 120 ms and each QRS is 80 ms in duration. Which of the following is the next most appropriate step in his management?

A. Amiodarone 400 mg by mouth
B. Diltiazem 10 mg IV
C. Enoxaparin 1 mg/kg
D. Metoprolol 5 mg IV
E. Metoprolol tartrate 25 mg by mouth

IV-41. You are evaluating Ms. Perry in your cardiology clinic. She is a 24-year-old woman who started to complain of postural light-headedness and palpitations a week or so after recovering from a mild upper respiratory illness. Her examination and sitting vital signs are normal. However, 2 minutes after standing, her heart rate is 135 beats/min and blood pressure is unchanged. Which of the following is a reasonable therapeutic option?

A. Compression stockings
B. Oral fludrocortisone
C. Oral midodrine
D. Sodium chloride tablets
E. Any of the above

IV-42. You are rounding on a 46-year-old man who is admitted to the hospital for bacterial pneumonia. While you are rounding, his heart rate rises to 230 beats/min and he feels a bit light-headed. Blood pressure is 110/88 and the rhythm strip from lead V_1 is shown in Figure IV-42. Which of the following is most likely to lead to sustained improvement in heart rate?

A. Adenosine 6 mg IV
B. Carotid body massage
C. Insertion of a single chamber pacemaker
D. Metoprolol tartrate 5 mg IV followed by 25 mg PO
E. Valsalva maneuver

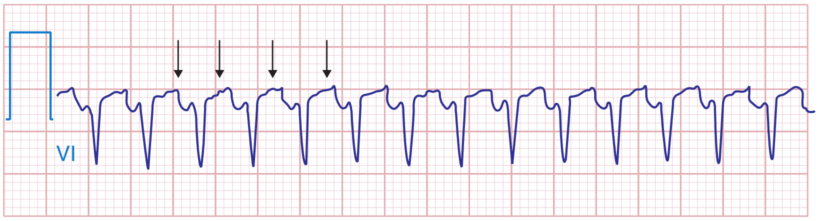


FIGURE IV-42 Adapted with permission from Longo DL et al: *Harrison's Principles of Internal Medicine*, 18th ed. New York: McGraw Hill, 2012.

IV-43. You are seeing a retired electrician in your clinic, Mr. Surish. He is a 72-year-old with no past medical history other than well-treated hypertension and presents today with complaints of occasional palpitations. You obtain a 12-lead electrocardiogram, which serendipitously occurs during one of his events. You note a rapid heart rate of 160 beats/min, a narrow QRS complex, and P waves with an abnormal axis occurring before every QRS. You astutely diagnose an atrial tachycardia. Which of the following is true about atrial tachycardia?

A. Atrial tachycardia can occur in the absence of structural heart disease.
B. Atrial tachycardia is the most common etiology of supraventricular tachycardia.
C. Atrial tachycardia occurs most often in people younger than age 50.
D. Fibrosis in atrial tissue is preventative against atrial tachycardia by preventing reentrant circuits.
E. Parasympathetic stimulation is a stimulating factor for atrial tachycardia.

IV-44. You are magically shrunken to the size of a cardiomyocyte and allowed to go on a "physiology safari" in a heart of a willing subject (do not ask how). While exploring the atrial tissue, you note that the patient goes into a tachycardia driven by a group of cells in the left atrium with enhanced automaticity. This focal group of cells is spontaneously depolarizing at a rate of 160 beats/min. Which of the following would you expect regarding this arrhythmia?

A. A "cool-down" phase is common prior to termination in this arrhythmia.
B. The arrhythmia will terminate immediately after giving adenosine to the patient.
C. The QRS complex in this rhythm would appear wide (>120 ms) on a surface, 12-lead electrocardiogram.
D. This rhythm relies on the atrioventricular node to continue.
E. This rhythm involves an accessory pathway between the atria and ventricles.

IV-45. Which of the following statements regarding the most common form of paroxysmal supraventricular tachycardia is true?

A. It is usually life-threatening.
B. It relies on enhanced automaticity as a mechanism.
C. It relies on multiple pathways for conduction from the atrium into the atrioventricular node.
D. It requires systemic anticoagulation for thromboembolic prophylaxis.
E. On the surface electrocardiogram, the P wave will appear prior to the R wave with a normal PR interval in this rhythm.

IV-46. You are caring for a 4-year-old boy after repair of muscular ventricular septal defect; he is postoperative day number 1 and doing well. The nurse pages you that he suddenly had a rise in heart rate. Given your clinical savvy and knowledge gleaned from hours of study, you suspect junctional ectopic tachycardia (JET). All of the statements regarding JET are true EXCEPT:

A. Isoproterenol administration may induce JET.
B. It is due to reentry within the atrioventricular node (AV).
C. It is more common in children.
D. It may commonly be seen after cardiac surgery or ablation procedures in the AV node.
E. It usually presents as a narrow complex tachycardia.

IV-47. You are seeing a young girl for failure to thrive. On the surface electrocardiogram she has a very short PR interval and slurred upstrokes of the QRS. You suspect an accessory conduction pathway. Which of the following diseases is associated with accessory pathways?

A. Danon disease
B. Ebstein anomaly
C. Fabry disease
D. Hypertrophic cardiomyopathy
E. All of the above

IV-48. You are on call in the emergency department when suddenly you hear the code bell. You rush to the room to find a new arrival, Ms. M. She is a 19-year-old who was out for a jog with a friend when she suddenly and inexplicably passed out. On your arrival, she is unresponsive and pulseless. A 12-lead electrocardiogram is shown in Figure IV-48. Which of the following rhythms is the cause of her cardiac arrest?

A. Atrial flutter
B. Atrial fibrillation with pre-excitation
C. Atrioventricular nodal reentrant tachycardia
D. Monomorphic ventricular tachycardia
E. Torsades de pointes

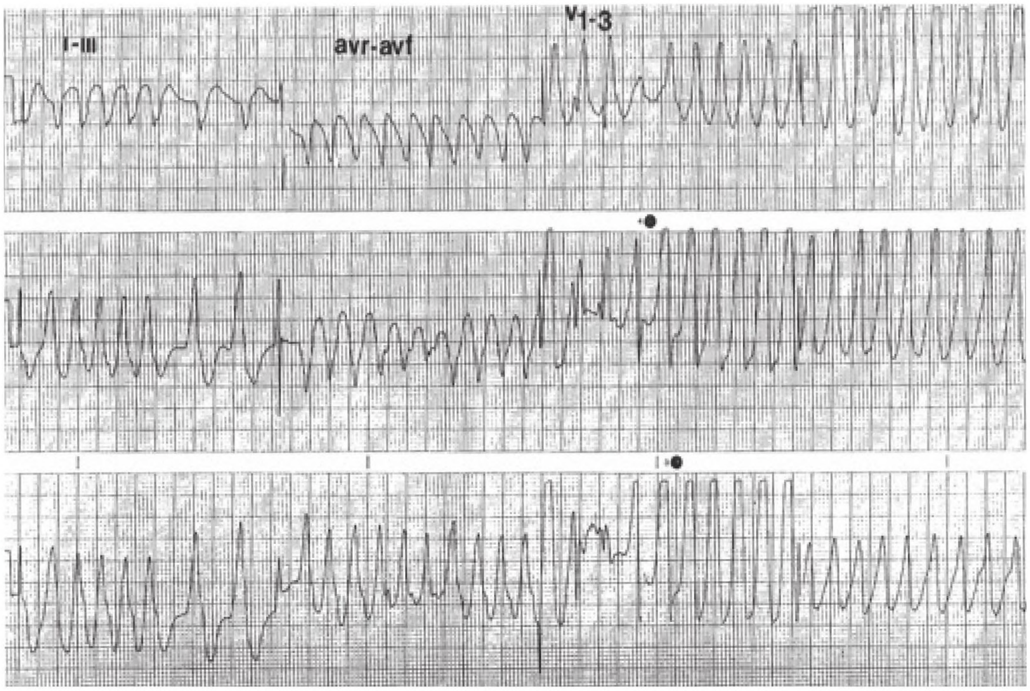


FIGURE IV-48

IV-49. In the patient described in question IV-48, which of the following medications is absolutely contraindicated in this situation?

A. Adenosine
B. Amiodarone
C. Diltiazem
D. Metoprolol
E. All of the above

IV-50. You are seeing Mr. Joe Murrow. He is a man from rural Georgia who has atrial flutter. You confirm the presence of atrial flutter on his surface electrocardiogram. Which of the following is true of *typical* or *common* atrial flutter?

A. Anticoagulation for thromboembolic prophylaxis is never required.
B. It is dependent on the cavotricuspid isthmus for conduction.
C. It usually is associated with a ventricular rate of approximately 80–100 beats/min.
D. The wave of depolarization propagates clockwise when viewed looking toward the tricuspid valve from the ventricular apex.
E. Vagal maneuvers will lead to increased ventricular rate.

IV-51. Which of the statements regarding the treatment of atrial flutter is true?

A. Catheter ablation has a high success rate in common atrial flutter.
B. Electrical cardioversion is never warranted.
C. Rate control is often more easily achieved in atrial flutter than in atrial fibrillation.
D. The most reasonable therapeutic strategy for the first presentation of atrial flutter is rate control.
E. The risk of cardioembolic events is lower in atrial flutter than in atrial fibrillation.

IV-52. Mr. Grady Stein is referred to you for atrial fibrillation. You assess his electrocardiogram and determine that he indeed has the characteristic irregularly irregular rhythm with an absence of notable P waves. Which of the following is true regarding the epidemiology of atrial fibrillation?

A. Incidence decreases with age.
B. More common in men than in women.
C. It is not associated with an increased risk of mortality.
D. It is not more common in people with a past medical history of hypertension.
E. All of the above are true.

IV-53. The clinical consequences of atrial fibrillation are attributable to which of the following pathophysiologic mechanisms?

A. Loss of atrial contraction
B. Predisposition to thrombus formation in the left atrial appendage with potential embolization
C. Rapid ventricular rate
D. All of the above
E. None of the above

IV-54. Mr. Alexander Beaux is an 86-year-old man with long-standing heart failure. He presents with the acute onset of palpitations, weakness, dizziness, and dyspnea. On arrival, his skin is cool and clammy, and he is sleepy. He will arouse to a loud voice, but he is not oriented and quickly becomes obtunded. His heart rate is irregularly irregular at 160 beats/min and his blood pressure is 50/30. STAT 12-lead electrocardiogram confirms atrial fibrillation with rapid ventricular response. Which of the following is the most reasonable next therapeutic step?

A. 200-J QRS-synchronous shock
B. Adenosine 6 mg IV
C. Digoxin 500 mcg IV
D. Metoprolol 5 mg IV
E. Transcutaneous pacing at 80 beats/min

IV-55. You are caring for Ms. Sarma, a 22-year-old woman with rheumatic mitral stenosis. She presents to your office with worsening dyspnea and you note that she is in atrial fibrillation. She is unclear when exactly her symptoms started. You calculate her CHA_2DS_2-VASc score as only 1 (for female "Sex Category"). Which of the following represents the appropriate approach to stroke prevention?

A. Arrange for immediate cardioversion to sinus rhythm
B. Initiate amiodarone orally and 1 week later arrange electrical cardioversion
C. Initiate aspirin 325 mg daily
D. Initiate apixaban 5 mg twice daily
E. Initiate warfarin

IV-56. Ms. Handrew presents with complaints of occasional palpitations. Her rhythm strip (Figure IV-56) is most consistent with which of the following rhythms?
A. Atrial flutter with variable conduction
B. Multifocal premature ventricular contractions
C. Nonsustained ventricular tachycardia
D. Normal rhythm
E. Sustained ventricular tachycardia

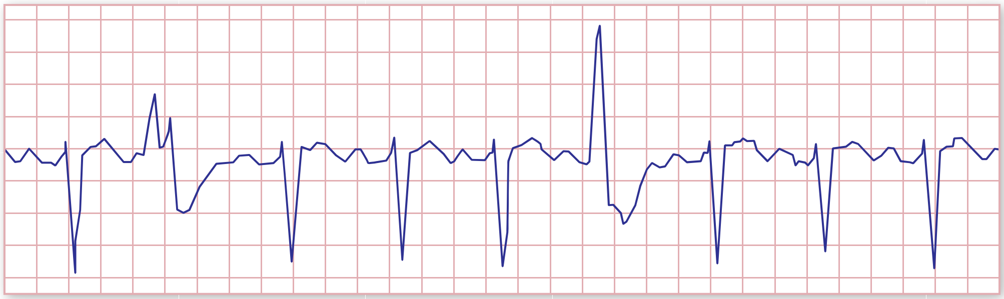


FIGURE IV-56

IV-57. Which of the following anti-arrhythmic medications is correctly matched to its primary mechanism of action?

A. Diltiazem—dihydropyridine calcium channel blockade
B. Flecainide—potassium channel blockade
C. Metoprolol—sodium channel blockade
D. Sotalol—delayed rectifier potassium channel blockade
E. Verapamil—β-adrenergic receptor blockade

IV-58. Mrs. Kappuli is a 25-year-old long distance runner who presents with occasional palpitations. She has had some increased stress at work and has been pulling long hours and relying increasingly on coffee to help stay awake. On a 12-lead ECG, you see normal sinus rhythm with two wide QRS complexes occurring earlier than the usual RR interval. You correctly diagnose premature ventricular contractions (PVCs). Which of the following statements regarding PVCs is true?

A. During myocardial ischemia, the presence of PVCs is not associated with future sustained ventricular tachycardia.
B. It is impossible to localize the anatomic site of PVC origin from a surface 12-lead ECG.
C. PVCs with a dominant R wave in lead V_1 originate from the right ventricle.
D. The presence of multiple morphologies of PVCs is less likely to indicate structural heart disease.
E. The QRS morphology can suggest whether structural heart disease is present or absent.

IV-59. You are evaluating Mr. Jenhiavi, a 45-year-old man with no past medical history. He has now had two episodes where he suddenly passed out without any prodromal symptoms. He presents to the office with no complaints other than this. On careful family history, you discover a father that died suddenly in his late 30s and a paternal uncle who was found dead in his house in his 40s. Surface electrocardiogram (ECG) for Mr. Jenhiavi (leads V_1–V_3) are shown in Figure IV-59.

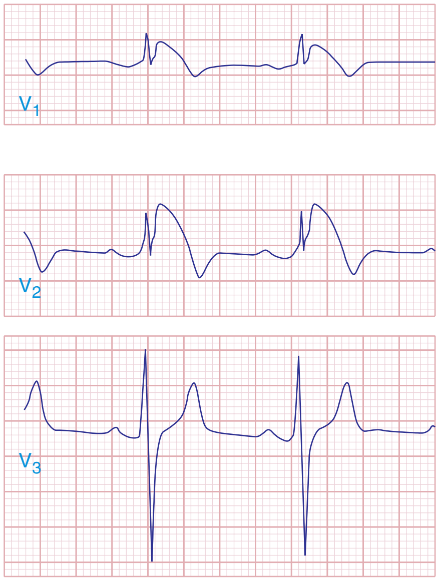


FIGURE IV-59

What disease is the ECG most consistent with?

A. Arrhythmogenic right ventricular cardiomyopathy.
B. Brugada syndrome.
C. Hypertrophic cardiomyopathy.
D. Long QT syndrome.
E. No disease, this is a normal variant ECG pattern.

IV-60. Mr. Ted Ford is admitted with an anterior myocardial infarction after watching his beloved college football team lose again. He undergoes timely revascularization with a stent to the left anterior descending artery. In the intensive care unit afterward, you notice frequent premature ventricular contractions but no ventricular tachycardia. You draw a set of electrolytes that finds a potassium of 3.2 mEq/L (normal 3.5–5.1) and magnesium of 1.1 mEq/L (normal 1.3–3.1). All of the following are indicated in this setting EXCEPT:

A. IV lidocaine.
B. Magnesium repletion.
C. Metoprolol.
D. Potassium repletion.
E. All of the above are indicated.

IV-61. You are rounding on Mr. Gary Booth, a 64-year-old man with cardiomyopathy with a left ventricular ejection fraction of 25% (normal ≥55%). He has been having frequent salvos of nonsustained ventricular tachycardia. Which of the following anti-arrhythmic medications has been shown to reduce his overall mortality in this setting?

A. Amiodarone
B. Dofetilide
C. Flecainide
D. Propafenone
E. None of the above

IV-62. Mr. Winters is a 67-year-old with a prior myocardial infarction and left ventricular dysfunction. He presents to the emergency department (ED) with a sudden feeling of light-headedness. On arrival to the ED, he is found to be tachycardic with a heart rate of 170 beats/min. A 12-lead electrocardiogram shows a wide complex, regular tachycardia. Which of the following features would make supraventricular tachycardia (SVT) more likely than ventricular tachycardia with aberrancy?

A. Findings consistent with atrioventricular dissociation.
B. No R wave in lead aVR.
C. Presence of a monomorphic R wave in leads V_1–V_6.
D. The presence of structural heart disease.
E. All of the above are associated with SVT.

IV-63. You are seeing Ms. Carvella who is a 35-year-old woman with no past medical history prior to 1 month ago when she was admitted to the local hospital last month with syncope. While in the emergency department, she had cardiac arrest due to monomorphic ventricular tachycardia with a left bundle branch block morphology. She was resuscitated and underwent coronary angiogram that showed normal coronary arteries. Echocardiogram showed normal left ventricular function. Leads V_1–V_3 done in the office today are shown in Figure IV-63A.

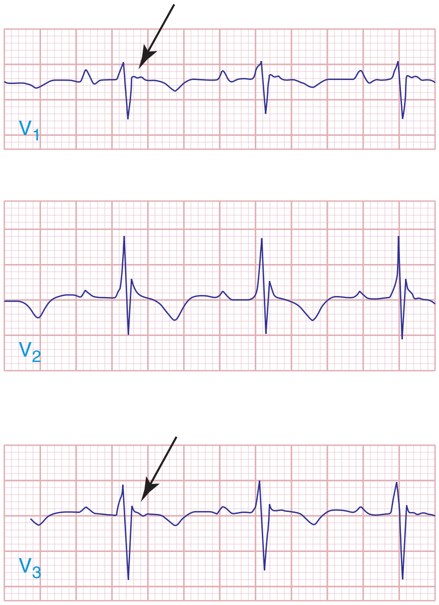


FIGURE IV-63A

A mutation in which of the following proteins is most likely to be responsible for her presentation?

A. β-Adrenergic receptors
B. Desmosomal proteins
C. Potassium channels
D. Sarcomere proteins
E. Sodium channel

IV-64. Mr. Steinberg is a 28-year-old with no past medical history. He is an avid singer in his local quartet but often gets nervous during his solo portions of the song. He reports palpitations during those episodes and he presents for assessment of these palpitations. To recapitulate the symptoms, you start a continuous 12-lead electrocardiogram and ask him to sing a solo to your office staff. During his solo he suddenly has the onset of monomorphic ventricular tachycardia (VT) with a left bundle branch morphology and large R waves in leads II, III, and aVF, and the rhythm spontaneously resolves. Echocardiogram and subsequent cardiac MRI are normal. Based on this presentation, you strongly suspect the VT is due to which of the following?

A. Arrhythmogenic right ventricular cardiomyopathy
B. Hypertrophic cardiomyopathy
C. Left ventricular outflow tract VT
D. Right ventricular outflow tract VT
E. Scar-mediated reentrant VT

IV-65. You are on call in the cardiac intensive care unit when you are called to the emergency department for a young patient in arrest. On arrival, you note that the electrocardiogram shows ventricular tachycardia (VT) with an odd, alternating QRS morphology. You diagnose bidirectional VT and suspect catecholaminergic polymorphic VT. Mutations in which protein are responsible for this deadly arrhythmia?

A. Calcium ryanodine receptor
B. Desmosomal proteins
C. Potassium channel
D. Sarcomeric proteins
E. Sodium channel

IV-66. You are called to the room of an unresponsive 78-year-old. Rhythm strip is shown in Figure IV-66. He is pulseless.

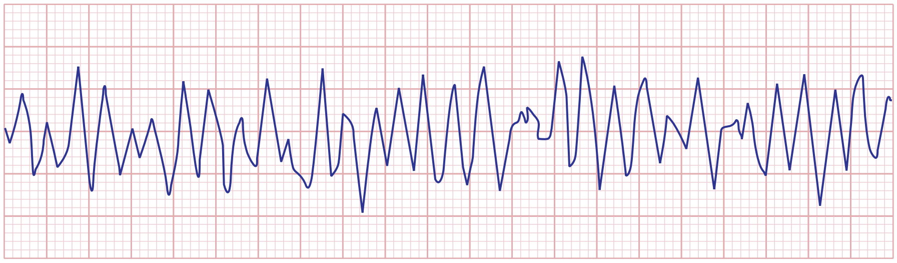


FIGURE IV-66

The most correct first action is which of the following?

A. Administer 100% oxygen by nonrebreather face mask
B. Administer 5 mg IV metoprolol
C. Administer procainamide IV
D. Administer 1 g calcium gluconate IV
E. Unsynchronized defibrillation with 200 J

IV-67. Mr. Kasper calls you to report shocks from his implantable cardioverter defibrillator (ICD). He has a long history of cardiomyopathy and is on metoprolol, lisinopril, aspirin, and eplerenone. He had been feeling well until this afternoon when he received three shocks within 15 minutes and then a fourth shock about 1 hour later. He says that other than feeling sore, he feels fine now. Which of the following is the most appropriate course of action?

A. Call emergency medical responders urgently to be transported to the emergency department for assessment.
B. Come into the clinic tomorrow for labs and an ICD interrogation.
C. Prepare a remote transmission for ICD interrogation.
D. Present to the local lab urgently to assess electrolytes.
E. Schedule left heart catheterization for next week to assess for new ischemic disease.

IV-68. A 68-year-old man with a history of myocardial infarction and congestive heart failure is comfortable at rest. However, when walking to his car, he develops dyspnea, fatigue, and sometimes palpitations. He must rest for several minutes before these symptoms resolve. Which of the following is his New York Heart Association classification?

A. Class I
B. Class II
C. Class III
D. Class IV
E. Class V

IV-69. A 47-year-old post-menopausal woman is seen for onset of severe dyspnea over the last few weeks. She reports no preceding chest pain, cough, sputum, or fever, although she does report leg swelling. Physical examination is notable for a blood pressure of 145/78 and heart rate of 123 beats/min. Exophthalmos is present as well as bilateral inspiratory crackles approximately occupying one-third of the lower chest with neck vein distention. She has a third heart sound with no murmur. Bilateral lower extremity edema is also present with warm extremities and a fine hand tremor. Which of the following is the most likely pathophysiologic explanation for her heart failure?

A. Anemia with high-output state
B. Chronic systemic hypertension with resultant left ventricular hypertrophy and non-systolic heart failure
C. Hemochromatosis with subsequent restrictive cardiomyopathy
D. Myocardial infarction with depressed left ventricular systolic function
E. Thyrotoxicosis with high-output state

IV-70. From a pathophysiologic perspective, all of the following are upregulated in heart failure with reduced ejection fraction EXCEPT:

A. Angiotensin II
B. B-type natriuretic peptide
C. Calcium uptake into the sarcoplasmic reticulum
D. Norepinephrine
E. Tumor necrosis factor

IV-71. A 67-year-old man presents to the emergency department with shortness of breath. He is found to have an elevated serum B-type natriuretic peptide (BNP). In addition to heart failure, all of the following may also cause an elevation in BNP EXCEPT:

A. Advanced age
B. Female gender
C. Obesity
D. Pulmonary embolism with right heart strain
E. Renal insufficiency

IV-72. You are taking care of a 72-year-old who suffered a myocardial infarction with late and unsuccessful revascularization. You appropriately prescribe guideline-directed medical therapy to the patient, but he is noncompliant. On your first visit, his left ventricle is 5.1 cm in diameter at end diastole with an ejection fraction of 40%. However, he returns after 2 years (having not taken his medications) and echocardiogram reveals that his left ventricle is 7.2 cm in diameter at end diastole and his ejection fraction is 25%. All of the following mechanisms are likely responsible for the remodeling of the left ventricle EXCEPT:

A. Abnormal myocardial energetics and metabolism
B. Alterations in the contractile properties of the myocyte
C. Increased β-adrenergic sensitization
D. Myocyte hypertrophy
E. Progressive loss of myocytes through necrosis, apoptosis, and autophagic cell death

IV-73. Which of the following statements regarding orthopnea is true?

A. It can be caused by abdominal obesity.
B. It does not improve with upright posture.
C. It occurs due to redistribution of blood from the central circulation to the peripheral and splanchnic circulations.
D. It usually occurs earlier than exertional dyspnea in the course of heart failure progression.
E. Nocturnal cough due to heart failure is not mechanistically related to orthopnea.

IV-74. Which of the following can be a symptom of heart failure?

A. Confusion
B. Early satiety
C. Nocturia
D. Right upper quadrant pain
E. All of the above

IV-75. Mr. George is a 52-year-old man with long-standing hypertension and poorly controlled diabetes. He presents complaining of several months of breathlessness with exertion, acute episodes of shortness of breath when recumbent, and lower extremity edema. On examination, he has an elevated jugular venous pulse and an S_4 on auscultation. Echocardiography shows a left ventricular ejection fraction of 55% with a large left atrium. You suspect this patient has the syndrome of heart failure with preserved ejection fraction (HFpEF). Drugs targeting which of the following has convincingly demonstrated mortality reduction for patients with HFpEF?

A. Angiotensin-converting enzyme inhibitors
B. Angiotensin receptor blockers
C. Phosphodiesterase-5
D. Sodium-potassium-ATPase
E. None of the above

IV-76. You are evaluating a 64-year-old woman with a history of nonischemic cardiomyopathy. She presents to the emergency department for shortness of breath. You note that she has gained 11 kg since her last cardiology appointment 2 months ago. Physical examination confirms findings associated with acute decompensated heart failure, such as pulmonary rales, elevated jugular venous pulse, abdominal ascites, lower extremity edema, and a square wave blood pressure Valsalva response. Her extremities are warm, and blood pressure is 110/78 with a heart rate of 75 beats/min. Her laboratory studies return with a sodium of 128 mEq/L and creatinine of 2.5 mg/dL (which is increased from her prior level of 1.2 mg/dL). Chest x-ray shows a diffuse alveolar filling pattern consistent with pulmonary edema. Which of the following is the most appropriate next step?

A. Administer digoxin, 250 mcg IV.
B. Administer furosemide 40 mg IV.
C. Insert a large bore central IV line and prepare for ultrafiltration.
D. Insertion of a pulmonary artery catheter for hemodynamic monitoring.
E. Start dobutamine at 5 μg/kg per minute and titrate to a urine output of 1 mL/kg per hour.

IV-77. Mr. Jones is a 21-year-old man who presents to the emergency room with several days of worsening shortness of breath and lethargy after 1 week after a viral upper respiratory tract infection. His family brought him in after he lacked the energy to rise from the couch unassisted. His blood pressure is 88/72, heart rate is 115 beats/min, and room air oxygen saturation is 90%. Physical examination reveals pulmonary crackles, elevated jugular venous pressure, an audible S_3 gallop, and cool extremities. He is lethargic and slow to respond to questions. Laboratory analysis reveals a creatinine of 2.3 mg/dL, elevated B-type natriuretic peptide level, and mildly elevated lactate. Bedside echocardiography reveals a left ventricular ejection fraction of 15% with global hypokinesis. You start dobutamine at 5 μg/kg per minute and prepare to insert a pulmonary artery catheter for hemodynamic monitoring. Before starting dobutamine, which of the following hemodynamic parameters is most likely increased and should decrease with therapy?

A. Cardiac output
B. Left ventricular stroke work index
C. Mixed venous oxygen saturation
D. Stroke volume
E. Systemic vascular resistance

IV-78. You are seeing a 72-year-old woman with a history of ischemic cardiomyopathy and left ventricular ejection fraction of 35%. She is New York Heart Association class II in terms of symptoms. She is on lisinopril 40 mg daily, carvedilol 25 mg twice daily, and spironolactone 25 mg daily. Her blood pressure is 102/82 and heart rate is 60 beats/min. Which of the following additional medications will further reduce her mortality?

A. Aliskiren
B. Digoxin
C. Ivabradine
D. Valsartan
E. None of the above

IV-79. You are seeing Mr. Jones, a 65-year-old former professional golfer, who you suspect has heart failure. Which of the following findings is LEAST LIKELY to be present on your evaluation?

A. An elevated jugular venous pulse
B. An enlarged pulsatile liver
C. A low-pitched heart sound occurring early after S_2
D. A normal 12-lead electrocardiogram
E. Peripheral edema

IV-80. You are seeing Mr. Ataley who is a 54-year-old man with dyspnea. After careful physical examination, you suspect cor pulmonale and pulmonary hypertension. Which of the following tests is required to definitively confirm the diagnosis of pulmonary hypertension and rule out left heart disease as causal?

A. B-type natriuretic peptide
B. Electrocardiogram
C. Exercise stress test
D. Right heart catheterization
E. Transthoracic echocardiogram

IV-81. A 22-year-old college student with no past medical history was seen in the urgent care clinic 3 days ago for coryza, myalgias, cough, and fever, which was typical of the viral upper respiratory illness making its way through the campus. He was given a cough suppressant and antipyretics and advised to remain hydrated. Today, he presents to the emergency department with lethargy and fatigue. He is obtunded with a heart rate of 120 beats/min and blood pressure of 78/62. His extremities are cool and his jugular venous pulse is elevated nearly to the mandible. Precordial auscultation reveals very quiet heart sounds, an S_3 gallop, and a soft murmur of mitral regurgitation. Emergent transthoracic echocardiogram shows no pericardial effusion, a non dilated left ventricle with an ejection fraction of 30%, and mild mitral regurgitation. Endomyocardial biopsy shows lymphocytic myocarditis. Which of the following statements regarding this patient's prognosis and implications for therapy are true?

A. His chance of survival is <10% without cardiac transplant—emergent transplant listing is warranted.
B. His chance of survival is >50% with many similar patients having a full recovery in left ventricular function over the ensuing weeks to months. Aggressive pharmacologic and mechanical hemodynamic support is warranted.
C. Immunosuppression with high-dose systemic steroids will increase his chance of survival.
D. The presence and titer of anti-heart antibodies can help provide prognostic information for this patient.

IV-82. You are evaluating a 42-year-old woman with a history of Hashimoto thyroiditis who many years ago was treated successfully with radioactive iodine. She presents to the emergency department (ED) after passing out briefly at home. She is awake in the ED and reports several days of worsening lethargy and chest discomfort. She is short of breath with a resting heart rate of 110 beats/min and blood pressure of 77/62. Her extremities are cool and she seems sleepy. Her whole blood lactate is elevated and urine output for the first 2 hours of her stay is minimal. On cardiac monitor, she repeatedly has salvos of nonsustained ventricular tachycardia. Echocardiogram reveals a left ventricular ejection fraction of 15%, and an emergent endomyocardial biopsy shows diffuse granulomatous lesions surrounded by extensive inflammatory infiltrate. Which of the following is true regarding her diagnosis?

A. Most patients with this etiology of cardiomyopathy recover with supportive care.
B. Steroids are highly effective in treating this form of cardiomyopathy.
C. The course of this cardiomyopathy is dire, often with rapid deterioration requiring urgent transplantation.
D. While seen occasionally, ventricular tachyarrhythmias are rare in this disease.
E. None of the above.

IV-83. All of the following are a risk factor for development of peripartum cardiomyopathy EXCEPT:

A. Advanced maternal age
B. Malnutrition
C. Primiparous
D. Twin pregnancy
E. Use of tocolytics

IV-84. You are evaluating a new patient in the clinic. The 25-year-old patient was diagnosed with "heart failure" in another state and has since relocated. He has New York Heart Association class II symptoms and denies angina. He presents for evaluation and management. On review of systems, the patient has been wheelchair bound for many years and is unable to walk. He has no family history of hyperlipidemia. His physical examination is notable for elevated jugular veins, bilateral lung crackles, an S_{33}, and generalized weakness more notable in the lower extremities. An electrocardiogram is obtained in the clinic and shows tall R waves in V_1 and V_2 with deep Qs in V_5 and V_6. An echocardiogram reports severe global left ventricular dysfunction with reduced ejection fraction. What is the most likely diagnosis?

A. Amyotrophic lateral sclerosis
B. Atrial septal defect
C. Chronic thromboembolic disease
D. Duchenne muscular dystrophy
E. Ischemic cardiomyopathy

IV-85. You admit a 19-year-old with acute-onset heart failure and left ventricular dysfunction. After assessment, you suspect acute viral myocarditis, which is confirmed on endomyocardial biopsy. Which of the following therapies is recommended for treatment for acute viral myocarditis?

A. Ibuprofen
B. Lisinopril
C. Oseltamivir
D. Prednisone
E. Thymoglobulin

IV-86. The pathogen responsible for Chagas disease is spread by which of the following insect vectors?

A. *Anopheles* mosquito
B. Common louse
C. Deer tick
D. Lone star tick
E. Reduviid bug

IV-87. You are seeing Mr. Whaley in the clinic today. He is a 67-year-old Caucasian man with no past medical history. He has symptoms of heart failure with orthopnea and limited exercise tolerance. On a 12-lead electrocardiogram he has both PR prolongation and multifocal premature ventricular contractions. Echocardiogram shows dilated left ventricular size and reduced function. Endomyocardial biopsy shows noncaseating granulomas. Which of the following is the most likely diagnosis?

A. Cardiac sarcoidosis
B. Chagas disease
C. Eosinophilic myocarditis
D. Lyme myocarditis
E. Tuberculous myocarditis

IV-88. Mr. Jones is a 28-year-old man who presents to the emergency department for dyspnea on exertion. He is now 5 years after an orthotopic heart transplant for nonischemic cardiomyopathy, and in general he has done quite well except for one cytomegalovirus reactivation within the first year. He reports that for the past 3 months, he has noticed that with decreasing amounts of exertion, he has been having limiting dyspnea. He is adamant that he is experiencing no chest pain or pressure during these episodes. He has been perfectly compliant with his regimen of tacrolimus, mycophenolate mofetil, and low-dose prednisone. Echocardiography reveals a normal left ventricular function with normal left ventricular wall thickness. His electrocardiogram shows normal sinus rhythm at a rate of 80 beats/min. Which of the following is the most likely cause of his symptoms?

A. Antibody-mediated rejection
B. Cellular rejection
C. Coronary artery disease
D. Endocarditis
E. Medication side effect

IV-89. You are seeing Ms. Block in the heart failure clinic. She is a 68-year-old woman with a past history of diffuse large B-cell lymphoma treated successfully with chemotherapy and eventual bone marrow transplant 15 years before. Unfortunately, she suffered chemotherapy-related cardiomyopathy and now has an ejection fraction of 15%. She has been hospitalized four times in the last 6 months with acute decompensated heart failure. She is currently New York Heart Association class III to IV from a symptom standpoint. Recently, she underwent a cardiopulmonary exercise stress test documenting a peak oxygen consumption of 9 mL/kg per minute. She is on optimal medical therapy. At a multidisciplinary transplant meeting, she was deemed not to be a candidate for orthotopic heart transplant due to her age and prior malignancy. She asks what other options are available for her, as her number one priority is to live 3 more years to see her grandson graduate high school. Which of the following is an appropriate response to Ms. Block?

A. There are no other options for prolonging your life. We should consider palliative measures in the future.
B. Stem cell implantation has been shown to prolong life in patients with end-stage cardiomyopathy; we should consider that.
C. Left ventricular assist devices (LVADs) are available and can improve quality of life, but provide no survival benefit over optimal medical care.
D. LVADs have been shown to improve survival over the initial 2–5 years more than optimal medical therapy. We should consider evaluation for an LVAD.
E. We should set you up with a continuous infusion of milrinone, a medicine that can help your heart beat stronger.

IV-90. After a common heart transplant operation, a portion of which donor heart chamber will remain in the donor?

A. Coronary sinus
B. Left atrium
C. Left ventricle
D. Right atrium
E. Right ventricle

IV-91. You are caring for Mr. Howse who is a 33-year-old man with end-stage cardiomyopathy who underwent implantation of a left ventricular assist system with a Heartmate 3 (HM3) device. All of the following distinguish the Heartmate 3 from the previous generation Heartmate 2 (HM2) EXCEPT:

A. The HM3 has a fully magnetically levitated motor.
B. The HM3 has a valve in the outflow graft.
C. The HM3 has intrinsic motor speed alterations.
D. The HM3 has wider blood flow paths.
E. All of the above are differences between the HM3 and HM2.

IV-92. Mr. Belliard is an 82-year-old man you previously followed in the cardiology clinic. He was last seen 3 years ago, when he noted occasional syncope. Subsequent workup revealed severe calcific aortic stenosis, with an aortic valve area of 0.7 cm^2 and an aortic mean gradient of 45 mmHg. At that time, you recommended surgical aortic valve replacement. On the day of his operation, however, Mr. Belliard called to say he really did not feel quite sick enough to undergo open heart surgery, and he would be back in touch when he was ready. He missed all subsequent follow-up appointments. Today, he presents to the emergency department after several weeks of lethargy and dyspnea. His blood pressure is 82/68 and heart rate is 110 beats/min with an electrocardiogram showing sinus rhythm. His carotid impulse is weak and delayed, and his extremities are cool to the touch. You again appreciate an S_4 on auscultation and a III/VI late-peaking systolic murmur. His renal and liver function are now impaired, and urine output is poor. The cardiothoracic surgeon on call defers emergent surgical valve replacement due to his acute renal and hepatic injury. Which of the following would be a reasonable therapeutic option to improve Mr. Belliard's short-term perfusion to permit aortic valve replacement?

A. Atorvastatin 80 mg
B. Digoxin 250 mcg IV once and 125 mcg orally daily thereafter
C. Metoprolol 5 mg IV serial dosing targeting a resting heart rate of 60–70 beats/min
D. Percutaneous aortic balloon valvuloplasty
E. Phenylephrine continuous IV infusion titrated to a mean arterial pressure of >65

IV-93. Mrs. Treadwell is an 85-year-old former lawyer who presents with several months of accelerating dyspnea on exertion and lower extremity edema. On examination, you note a laterally displaced point of maximal impulse and an S_4 gallop. She has a III/VI systolic murmur at the base radiating to the carotid arteries. Transthoracic echocardiogram reveals a left ventricular ejection fraction of 25% with global hypokinesis. Calculated aortic valve area is 0.8 cm^2 with a mean gradient of 25 mmHg. What is the next most reasonable step to determine whether Mrs. Treadwell would benefit from aortic valve replacement?

A. Cardiac MRI to evaluate ventricular scar and aortic valve morphology
B. Cardiac positron emission tomography to determine ventricular viability
C. Coronary angiography to evaluate for the presence of obstructive coronary disease
D. Dobutamine stress echocardiography
E. Right heart catheterization to document cardiac output and filling pressures

IV-94. All of the following statements regarding bicuspid aortic valve (BAV) disease are true EXCEPT:

A. A mutation in the *NOTCH1* gene is responsible for BAV in some families.
B. Ascending aortic aneurysm formation occurs commonly among patients with BAV disease.
C. BAV has a female to male predominance.
D. BAV is the most common congenital heart abnormality.
E. All of the above are true.

IV-95. Which of the following physical examination findings are associated with severe aortic stenosis?

A. A delayed and weak carotid pulse
B. Augmentation of the murmur with Valsalva
C. Bounding femoral pulsation
D. Holosystolic murmur at the apex radiating to the axilla
E. Pan-cycle murmur at the apex

IV-96. Which of the following parameters is typically *reduced* in chronic severe aortic regurgitation?

A. Diastolic blood pressure
B. Left ventricular afterload
C. Left ventricular diameter
D. Left ventricular preload
E. Total left ventricular stroke volume

IV-97. You are caring for a new admission to the cardiac intensive care unit who is a 21-year-old with connective tissue disease. She presented with acute shortness of breath and a chest x-ray showing diffuse pulmonary edema. Physical examination revealed a soft, short early diastolic murmur at the right upper sternal border, and emergent echocardiography showed severe aortic regurgitation with an avulsed right coronary cusp. CT chest imaging showed no aortic dissection. On arrival to the cardiac care unit, she is intubated and sedated. Blood pressure is 110/50 and heart rate is 115 beats/min. Her urine output is poor and extremities are cool. The cardiothoracic surgical team is tied up in a heart transplant and will not be able to take this patient for at least 4 more hours. What intervention is most likely to help maintain her end-organ perfusion until surgical intervention?

A. Esmolol continuous IV infusion titrated to a heart rate of 60–70 beats/min
B. Intra-aortic balloon pump
C. IV nitroprusside
D. IV norepinephrine
E. Vasopressin IV

IV-98. All of the following physical examination findings are seen in aortic regurgitation EXCEPT:

A. A booming “pistol-shot” sound heard over the femoral arteries
B. A rapidly rising “water-hammer” pulse
C. A systolic crescendo-decrescendo murmur radiating to the carotids
D. A to-and-fro murmur audible over a lightly compressed femoral artery
E. Alternate flushing and paling of the skin at the root of the nails

IV-99. In cases of severe mitral stenosis, which of the following parameters is typically increased?

A. Cardiac output
B. Left atrial pressure
C. Left ventricular diameter
D. Left ventricular end diastolic pressure
E. Pulmonary vascular compliance

IV-100. Mrs. Bream presents to the emergency department with acute worsening of shortness of breath. She is an 84-year-old woman with severe mitral stenosis who is scheduled for percutaneous mitral balloon valvotomy in 3 days. However, today while cooking chicken salad, she noted the onset of overwhelming weakness and dyspnea. On evaluation, she appears dyspneic and in mild distress. Oxygen saturation on room air is 91%, heart rate is 55 beats/min, and blood pressure is 110/80. She has rales to the mid-lung fields bilaterally. You note that her rhythm is irregularly irregular, and electrocardiogram confirms the new onset of atrial fibrillation. You suspect that she has a very high left atrial pressure causing pulmonary edema. All of the following therapeutic interventions will help lower her left atrial pressure EXCEPT:

A. IV furosemide.
B. Percutaneous balloon mitral valvotomy.
C. Synchronized direct current cardioversion.
D. Transvenous pacemaker placement and pacing at a heart rate of 90 beats/min.
E. All of the above will help lower left atrial pressure.

IV-101. You are examining Mr. Cooper, a 45-year-old man who has largely avoided medical care thus far in his life. On examination, you note distended jugular veins and a soft decrescendo diastolic murmur at the apex. Point of maximal impulse is small and nondisplaced. You suspect mitral stenosis. Which of the following is the most common cause of mitral stenosis worldwide?

A. Infectious endocarditis
B. Mitral annular calcification
C. Rheumatic fever
D. Rheumatoid arthritis
E. Systemic lupus erythematosus

IV-102. You are seeing Mr. Garibalt who is a 56-year-old man with severe rheumatic mitral stenosis. During an exercise test he complains of shortness of breath. All of the following physiologic parameters will increase during his exercise test EXCEPT:

A. Diastolic filling time
B. Left atrial pressure
C. Mitral valve pressure gradient
D. Pulmonary arterial pressure
E. Pulmonary vascular resistance

IV-103. As a resident on rounds, your attending Dr. X. Pounds who is discussing whether a patient's mitral regurgitation (MR) is "primary" or "secondary." What is your attending talking about?

A. In primary MR the leaflets/chordae are responsible for abnormal valve function, whereas in secondary MR the valve dysfunction is usually caused by ventricular remodeling.
B. Primary MR occurs early (usually prior to age 18), whereas secondary MR occurs later in life.
C. Primary MR occurs only in prime number years, whereas secondary MR can occur in any year.
D. Primary MR is due to a congenital valvular abnormality, whereas secondary MR is not.
E. Primary MR is caused by infectious endocarditis, whereas secondary MR is not.

IV-104. All of the following are INCREASED in the setting of severe mitral regurgitation EXCEPT:

A. Left atrial pressure
B. Left atrial systolic volume
C. Left ventricular afterload
D. Left ventricular preload
E. Stroke volume

IV-105. You are seeing Mr. Washington, a 27-year-old former IV drug user (now clean for 5 years and doing very well in his abstinence) for dyspnea. His examination suggests severe mitral regurgitation and this is confirmed on echocardiogram. His left ventricular systolic function is normal and the consulting cardiothoracic surgeon feels that either mitral valve repair or replacement are technically feasible. His blood pressure is normal. Which of the following is the best course of therapy for Mr. Washington?

A. Initiate Lisinopril 10 mg daily.
B. No therapy now; repeat echocardiogram in 1 year.
C. Surgical mitral valve repair.
D. Surgical mitral valve replacement.
E. Transcatheter mitral valve repair.

IV-106. Which of the following statements regarding mitral valve prolapse (MVP) is true?

A. MVP is more common in connective tissue diseases such as Marfan syndrome or Ehlers-Danlos syndrome.
B. MVP occurs more commonly in men than in women.
C. The anterior leaflet is usually more affected than the posterior leaflet.
D. The clinical course of MVP is invariably pathologic and leads to symptoms.
E. The click and murmur of MVP will occur later with the initiation phase of Valsalva.

IV-107. Mrs. Avery is a 50-year-old woman with idiopathic pulmonary arterial hypertension. You are seeing her in the cardiology clinic as her primary care physician noted that her last transthoracic echocardiogram found severe tricuspid regurgitation in addition to a dilated hypokinetic right ventricle and pulmonary systolic pressures exceeding 70 mmHg. On your examination, she has lower extremity edema, hepatomegaly with a pulsatile liver, jugular venous pulse elevated to the mandible with marked c-v waves and a prominent y-descent, and a right ventricular heave. She reports breathlessness with moderate exertion. Which of the following is the best treatment for her severe tricuspid regurgitation?

A. Diuretics and salt restriction accompanied by medical therapy targeting her elevated pulmonary artery pressures
B. Surgical tricuspid valve repair
C. Surgical tricuspid valve replacement with a mechanical prosthesis
D. Percutaneous tricuspid valve repair
E. Percutaneous balloon valvotomy

IV-108. Which of the following is the most common cause of pulmonic valve stenosis?

A. Calcific degeneration
B. Carcinoid syndrome
C. Noonan syndrome
D. Obstructing tumors
E. Rheumatic fever

IV-109. Which of the following descriptors applies to pulmonic regurgitation but NOT aortic regurgitation?

A. Bounding peripheral pulses
B. Decrescendo murmur
C. Diastolic murmur
D. Murmur louder with inspiration
E. Wide systemic pulse pressure

IV-110. You are taking care of a 77-year-old patient with severe aortic stenosis in the cardiac intensive care unit. Surgical aortic valve replacement is planned for tomorrow. However, suddenly, he becomes severely short of breath and manifests signs of acute pulmonary edema. On auscultation, you can now appreciate a soft, short apical systolic murmur (in addition to his prior-appreciated murmur of aortic stenosis) that was not present previously. You suspect that he has suffered a ruptured mitral valve chordae and now has severe, acute mitral regurgitation. Which of the following parameters will likely increase due to his new severe mitral regurgitation?

A. Aortic valve gradient
B. Calculated aortic valve area
C. Effective stroke volume
D. Ejection fraction
E. Left ventricular afterload

IV-111. Which of the following statements regarding patients with mixed aortic stenosis (AS)/aortic regurgitation (AR) versus those with isolated aortic stenosis is true?

A. Preload will be lower with mixed AS/AR.
B. Transvalvular velocities will be lower with mixed AS/AR.
C. The Gorlin equation will be more accurate in mixed AS/AR.
D. The systolic component of the murmur will be louder with mixed AS/AR.
E. All of the above are true.

IV-112. All of the following are classic definitional features of the tetralogy of Fallot EXCEPT:

A. Obstruction to right ventricular outflow
B. Overriding aorta
C. Right ventricular hypertrophy
D. Tricuspid atresia
E. Ventricular septal defect

IV-113. You are evaluating a 21-year-old man in the clinic. He feels occasionally tired during his senior year of college, but he is otherwise asymptomatic. You first saw him 6 weeks ago and noted a harsh, holosystolic murmur at the left lower sternal border that augmented with hand grip. Suspecting a ventricular septal defect (VSD), you referred him for echocardiography, which confirmed your suspicion, visualizing a 5-mm VSD in the muscular interventricular septum. Subsequent right heart catheterization for hemodynamic assessment revealed a mean pulmonary artery pressure of 20 mmHg, pulmonary venous resistance of 2 Wood units, and systemic vascular resistance of 6 Wood units. Through meticulous serial measurements of venous oxygen saturations in the central veins and right heart, you calculate a right heart cardiac output of 7.5 L/min and systemic cardiac output of 6 L/min. Given these findings you recommend what therapeutic course?

A. Cardiopulmonary exercise testing to define peak oxygen consumption.
B. Closure with a percutaneously deployed septal occluder device.
C. Consideration of heart and lung transplant.
D. No intervention now; annual cardiology assessments and re-imaging if any new symptoms emerge.
E. Surgical correction via open heart surgery and patch repair.

IV-114. Which of the following statements regarding the epidemiology of congenital heart disease (CHD) in the United States is true?

A. CHD remains extremely rare, complicating 0.1% of all live births.
B. Given advances in surgical techniques and prenatal and postnatal care, survival for a neonate with CHD now approaches 90%.
C. Given the declining rates of pregnancy in women with CHD, the incidence of CHD in neonates is declining.
D. The population of adults with CHD is declining given improved prenatal screening efforts.
E. Women with CHD are at no greater risk for complication during pregnancy than the normal population.

IV-115. A 62-year-old man is being evaluated for mitral valve replacement surgery for severe mitral regurgitation. As part of his evaluation, he undergoes a transesophageal echocardiogram that demonstrates a small jet of right-to-left Doppler flow during systole across the atrial septum. The jet is located roughly in the middle of the septum and occurs when a small flap of tissue swings open <1 mm. There is no diastolic flow, nor is there a visible opening in any part of the septum during diastole. Which of the following explains the finding on echocardiography?

A. Ostium primum atrial septal defect
B. Ostium secundum atrial septal defect
C. Partial anomalous pulmonary venous return
D. Patent foramen ovale
E. Sinus venosus atrial septal defect

IV-116. Which of the following congenital cardiovascular abnormalities would provide highest maternal risk in the setting of pregnancy?

A. Bicuspid aortic valve with aortic diameter <45 mm
B. Partial anomalous pulmonary venous return without pulmonary hypertension
C. Severe native aortic coarctation
D. Systemic right ventricle
E. Unoperated atrial septal defect without pulmonary hypertension

IV-117. You are reading an echocardiogram on a 26-year-old with dyspnea and a murmur. You note a mid-septal ventricular septal defect. You also expect to find dilation of which of the following cardiac chambers?

A. Coronary sinus
B. Left atrium
C. Left ventricle
D. Right atrium
E. Right ventricle

IV-118. Mr. Ryan is a 32-year-old bass guitarist with no significant past medical history. He presents with chest pain after suffering coryza, cough, fever, and muscle aches for the past week. He describes his pain as constant, exacerbated by lying flat and deep breaths, and radiating to his left shoulder. Examination reveals a rasping extra-cardiac sound present in three components per heartbeat. His electrocardiogram is pictured in Figure IV-118. Troponin I levels are undetectable on presentation and 6 hours later. Blood pressure, heart rate, and oxygenation are normal. What is the most appropriate next step?

A. Aspirin 81 mg daily, metoprolol 25 mg twice daily, and atorvastatin 80 mg daily.
B. Aspirin 1 g every 8 hours with omeprazole 20 mg daily.
C. Prednisone 40 mg daily for 2 weeks followed by a taper over the ensuing 2 months.
D. Referral for transthoracic echocardiogram.
E. Start IV heparin, give high-dose aspirin and clopidogrel, and refer for emergent coronary angiography.

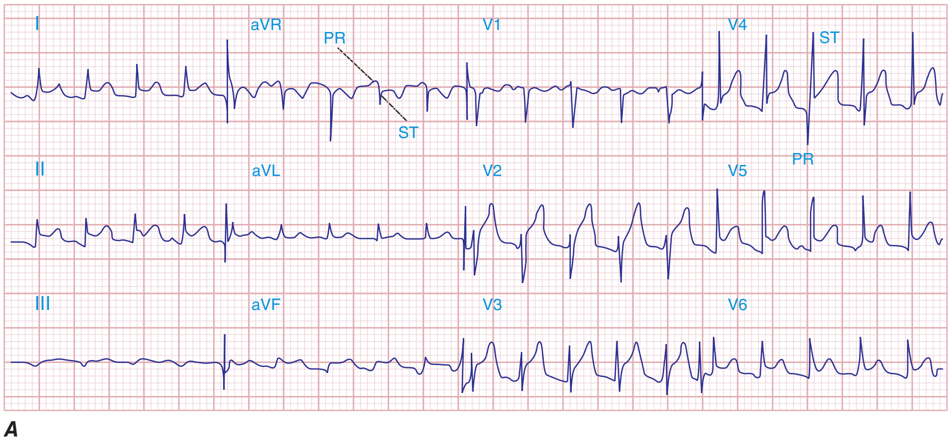


FIGURE IV-118

IV-119. A 35-year-old woman is admitted to the hospital with malaise, weight gain, increasing abdominal girth, and edema. The symptoms began about 3 months ago and gradually progressed. The patient reports an increase in waist size of ~15 cm. The swelling in her legs has gotten increasingly worse such that she now feels her thighs are swollen as well. She has dyspnea on exertion and two-pillow orthopnea. She has a past history of Hodgkin disease diagnosed at age 18. She was treated at that time with chemotherapy and mediastinal irradiation. On physical examination, she has temporal wasting and appears chronically ill. Her current weight is 96 kg, an increase of 11 kg over the past 3 months. Her vital signs are normal. Her jugular venous pressure is ~16 cm, and the neck veins do not collapse on inspiration. Heart sounds are distant. There is a third heart sound heard shortly after aortic valve closure. The sound is short and abrupt and is heard best at the apex. The liver is enlarged and pulsatile. Ascites is present. There is pitting edema extending throughout the lower extremities and onto the abdominal wall. Echocardiogram shows pericardial thickening, dilatation of the inferior vena cava and hepatic veins, and abrupt cessation of ventricular filling in early diastole. Ejection fraction is 65%. What is the best approach for treatment of this patient?

A. Aggressive diuresis only
B. Cardiac transplantation
C. Mitral valve replacement
D. Pericardial resection
E. Pericardiocentesis

IV-120. You admit Mr. Heyes who is a 45-year-old man undergoing treatment for metastatic adenocarcinoma of unknown primary origin. He is admitted with acute dyspnea. On arrival he is in distress. He is hypotensive to 70/30 and tachycardic to the 140s. Jugular veins are distended and his lungs are clear. Electrocardiogram shows low QRS voltage and sinus tachycardia, and you have to strain to hear his very quiet heart sounds on precordial auscultation. Which of the following is likely to be DECREASED in this patient?

A. Intrapericardial pressure
B. Jugular venous pressure
C. Left atrial pressure
D. Left ventricular end diastolic pressure
E. Left ventricular end diastolic volume

IV-121. Which of the following statements is true regarding cardiac tumors?

A. Benign cardiac tumors never require resection.
B. Primary cardiac tumors are much more common than secondary involvement with metastatic disease.
C. Primary cardiac tumors are usually malignant.
D. The most common primary sites from which cardiac metastases originate are carcinoma of the breast and lung.

IV-122. You are examining a 17-year-old man with slowly developing shortness of breath. On examination, you auscultate an early, low pitched “plopping” sound in diastole. Echocardiography reveals a spherical mass in the left atrium, attached to the atrial septum. Which of the following statements is true regarding this intracardiac mass?

A. Endomyocardial biopsy is warranted prior to resection.
B. Screening of family members is not required.
C. Surgical resection is required.
D. Treatment with radiation and chemotherapy should be initiated.
E. All of the above are true.

IV-123. Mr. Jackson is undergoing an exercise stress test. You know that as he progresses through his stress test his myocardium will require more oxygen. How does the normal (nondiseased) heart respond to meet its higher oxygen demand?

A. Increased myocardial oxygen extraction during near constant coronary blood flow
B. Increased oxygen extraction from the ventricular chambers
C. Relative expansion of the diastolic time period allowing increased coronary flow
D. Vasodilation of epicardial coronary arteries leading to decreased resistance and increased coronary blood flow
E. Vasodilation of intramyocardial coronary vessels leading to increased coronary blood flow

IV-124. As Mr. Jackson (from question IV-123) continues on his exercise stress test, he begins to complain of a pressure-like chest pain. You suspect that he is experiencing angina due to a partially occluded coronary artery. If you were able to immediately analyze the biochemical changes occurring in his ischemic myocardium, you would note all of the following EXCEPT:

A. An increase in cytosolic calcium
B. An increase in intracellular pH
C. A shift from aerobic to anaerobic metabolism
D. Depletion of myocardial stores of high energy phosphates
E. Leakage of potassium from myocytes

IV-125. Ms. Wilson is a 66-year-old post-menopausal United States postal employee. While walking her mail route over the past 9 months, she routinely has chest pressure and dyspnea while climbing a certain steep hill. The pressure resolves when she rests for about 3 minutes. She has not missed any work due to these symptoms. You suspect she is experiencing angina. What term and Canadian Cardiovascular Society (CCS) functional class of angina are appropriate to describe her symptoms?

A. Stable angina—CCS class I
B. Stable angina—CCS class II
C. Stable angina—CCS class III
D. Stable angina—CCS class IV
E. Unstable angina

IV-126. You are evaluating Mr. Washkansky, an 87-year-old man with only a history of hypertension. He reports classic exertional angina. On coronary angiography, you find no coronary artery disease with normal caliber vessels. You do note a 50-mmHg mean gradient across his aortic valve, however, with a calculated aortic valve area of 0.6 cm^2. Echocardiogram shows normal left ventricular systolic function with left ventricular concentric hypertrophy. Which of these physiologic processes explains Mr. Washkansky's angina?

A. Exertional arrhythmias
B. Mismatch in myocardial oxygen supply and demand
C. Pericarditis
D. Transient coronary artery vasospasm
E. None of the above

IV-127. You are caring for Mr. Hubble, a 65-year-old former astronomer. He is usually very active and is an avid tennis player. However, he reports that for the last year halfway through his fourth game of singles tennis he has to stop due to chest pain that sounds like classic angina. After 2 minutes, the angina subsides. This exertional limitation has been stable over the last year and he does not experience chest pain at other times. He is on no medications. You refer him for coronary angiography, which demonstrates a 70% stenosis in his mid-left anterior descending coronary artery. Left ventriculography shows normal ventricular systolic function. What is the next most reasonable course of action from those listed below?

A. Advise him to stop playing tennis.
B. Coronary arterial bypass grafting.
C. Initiate anti-anginal medical therapy with beta blocker, statin, and aspirin.
D. Percutaneous coronary intervention with a drug-eluting stent.
E. Percutaneous coronary intervention with a bare metal stent.

IV-128. Mr. Brian is a 57-year-old hockey team coach with a prior history of hypertension, hyperlipidemia, and tobacco abuse. He presents to the emergency department tonight after experiencing chest discomfort during a practice. He notes that he first began experiencing chest discomfort 3 weeks prior with vigorous exertion during practice. However, over the last week, it has taken less exertion to initiate the discomfort. Tonight, it occurred while he was just sitting on the bench. He describes the discomfort as a pressure, radiating to his jaw. It typically lasts about 10 minutes. His electrocardiogram shows new T wave inversions in leads I, II, aVL, V_5, and V_6 since his last cardiogram 2 years on a routine physical examination. Which of the following clinical entities is an appropriate diagnosis for Mr. Brian?

A. More information is required before making a diagnosis.
B. Non–ST-elevation myocardial infarction.
C. ST-elevation myocardial infarction.
D. Stable angina.
E. Unstable angina.

IV-129. Mr. Riviera is a 42-year-old man with anuric end-stage renal disease caused by diabetes mellitus. Due to recent car trouble, he missed his most recent dialysis appointment and presents to the emergency department with shortness of breath. His heart rate is 105 beats/min and blood pressure is 185/100. He has fine rales in the bilateral lower lung fields, and his jugular venous pulse is elevated. Electrocardiogram (ECG) shows sinus tachycardia without ST deviation. Initial troponin I assay returns at 0.14 ng/dL (normal is <0.06 ng/dL). Which of the following are the next most appropriate diagnostic and therapeutic steps?

A. Administer 80 mg of IV furosemide; follow serial troponin I values and ECGs.
B. Administer 80 mg aspirin; refer for pharmacologic nuclear stress testing.
C. Initiate dual antiplatelet therapy (aspirin and clopidogrel) and heparin; follow serial troponin I values and ECGs.
D. Initiate dual antiplatelet therapy (aspirin and clopidogrel) and heparin; refer for urgent coronary angiography.
E. Urgent hemodialysis with ultrafiltration for fluid removal; follow serial troponin I values and ECGs.

IV-130. A 67-year-old fry chef at the local Waffle Empire presents to the emergency department with the sudden onset of crushing substernal chest pain. He has a history of hypertension, hyperlipidemia, and erectile dysfunction for which he takes daily amlodipine, simvastatin, and tadalafil. On your evaluation, his blood pressure is 145/85 and heart rate is 90 beats/min. His lungs are clear and his jugular venous pulse is not elevated. There are no murmurs or gallops on cardiac auscultation. He continues to complain of chest discomfort, rating it an 8/10. Initial troponin I returns elevated at 0.52 ng/dL (normal <0.06 ng/dL) and electrocardiogram reveals 1-mm ST depression in II, III, aVF, V_5, and V_6. All of the following pharmacologic therapies are reasonable to administer EXCEPT:

A. Aspirin orally
B. Clopidogrel orally
C. Heparin IV
D. Metoprolol IV
E. Nitroglycerin sublingually

IV-131. You are seeing a 75-year-old man admitted to the hospital for non–ST-elevation myocardial infarction. He takes aspirin daily and has a prior history of myocardial infarction treated with a stent to the left anterior descending artery 5 years prior. He has had accelerating angina at least twice daily over the past 4 days and on admission has 1 mm of ST depression in leads II, III, and aVF and positive troponin biomarkers. All of the following details of his presentation confer increased risk of poor outcomes for this patient EXCEPT:

A. One anginal episode in 24 hours.
B. Age.
C. Daily aspirin use.
D. Prior history of coronary artery disease.
E. All of the above confer increased risk.

IV-132. You are seeing a 42-year-old woman with repeated presentations to the emergency department with chest pain. The pain usually has classic anginal qualities. On this presentation, she has transient ST elevations in leads V_1–V_4 as well as I and aVL that occurred with the pain. Troponin biomarkers are mildly elevated. On coronary angiography, she has no atherosclerosis. However, during the procedure when asked to hyperventilate, there is distinct vasospasm in the left anterior descending artery. All of the following are reasonable treatments for her EXCEPT:

A. Amlodipine
B. Aspirin
C. Atorvastatin
D. Diltiazem
E. Long-acting oral nitrates

IV-133. Mr. Gilroy is a 57-year-old oil rig worker with a history of hypertension, tobacco abuse, and diabetes mellitus. He presents to the emergency department with 30 minutes of crushing substernal chest pain, radiating to the jaw, and associated with profuse sweating and shortness of breath. His blood pressure is 115/90 and heart rate is 95 beats/min. What diagnostic test will provide the most rapid method of altering therapeutic management for Mr. Gilroy?

A. 12-lead electrocardiogram
B. Coronary CT angiography
C. Echocardiogram
D. Serum creatinine kinase-myocardial band level
E. Serum troponin I level

IV-134. You are performing a diagnostic coronary angiography on Mr. Hayes. On the initial angiographic pictures his arteries are clear of any obstructive disease. However, during a selective angiogram of the left anterior descending artery, you notice that a thrombus has formed on the tip of your catheter. During dye injection, the thrombus embolizes down the left anterior descending coronary artery causing complete obstruction to flow. You are fortunately able to remove the thrombus with suction thrombectomy almost immediately. If you had not been able to remove the thrombus, when would you first have expected detectable creatine kinase myocardial band isoform in a standard serum assay?

A. 5–10 minutes
B. 1–2 hours
C. 4–8 hours
D. 12–24 hours
E. 24–48 hours

IV-135. All of the following medications used in the acute management of ST-elevation myocardial infarction are appropriately matched to its mechanism of effect EXCEPT:

A. Aspirin—reduction in thromboxane A_2
B. Abciximab—inhibition of the glycoprotein IIb/IIIa receptor
C. β-Adrenergic antagonists—reduced myocardial oxygen consumption
D. Clopidogrel—inhibition of the platelet adenosine diphosphate receptor
E. Nitroglycerin—reduced cardiac afterload

IV-136. Mr. Cooper underwent tissue plasminogen activator administration for acute ST-elevation myocardial infarction 1 hour previously. He had an excellent response with resolution of his ST-segment elevation and chest pain; however, the nurse pages you to evaluate a change in his rhythm. You note a wide complex ventricular rhythm with a rate of 75 beats/min. Mr. Cooper continues to feel well without new symptoms and his blood pressure is 120/80. The next most appropriate therapeutic maneuver is which of the following?

A. Administer amiodarone 150 mg IV over 10 minutes
B. Administer flecainide 400 mg orally
C. Administer metoprolol 5 mg IV every 5 minutes × 3
D. Carotid sinus massage
E. Continue observation

IV-137. Which of the following medications should be avoided in patients with an acute ST-elevation myocardial infarction?

A. Aspirin
B. Colchicine
C. Glucocorticoids
D. Heparin
E. Metoprolol

IV-138. If no contraindications are present, fibrinolysis for ST-elevation myocardial infarction should be administered within how many minutes of presentation?

A. 30 minutes
B. 60 minutes
C. 90 minutes
D. 120 minutes
E. No time limit

IV-139. Approximately how long should patients with ST-segment elevation myocardial infarction be advised to maintain bedrest after revascularization?

A. 6–12 hours
B. 24 hours
C. 48 hours
D. 72 hours
E. 7 days

IV-140. Ms. Kella is a 48-year-old woman with a history of atrial fibrillation and peptic ulcer disease who is brought to your emergency department with 30 minutes of crushing substernal chest pain. Her blood pressure is 110/65 with an irregular heart rate of 85 beats/min and a resting room air oxygen saturation of 91%. Her electrocardiogram shows 3–4 mm ST-segment elevations in leads V_2–V_4. Your hospital is 4 hours from the nearest catheterization laboratory and the weather precludes an air transport. Her medications include warfarin, metoprolol, atorvastatin, and losartan. Which of the following is a clear contraindication to administering an IV thrombolytic agent?

A. Blood pressure of 110/65
B. History of a cerebrovascular hemorrhage 2 years ago
C. History of hypertension
D. History of peptic ulcer disease
E. Warfarin use

IV-141. Mrs. Heyward is an 84-year-old woman with a history of diabetes and hyperlipidemia. Three weeks ago she presented to the emergency department with an ST-elevation myocardial infarction and underwent emergent, primary percutaneous coronary intervention to an acutely occluded left anterior descending artery. A 3.5 × 24 mm everolimus-eluting stent was placed with excellent angiographic results and complete resolution of her symptoms. She has been feeling excellent since then. Her discharge medications were metoprolol, aspirin, clopidogrel, rosuvastatin, lisinopril, and sliding scale insulin. She recently went to see her ophthalmologist, Dr. Seewell, who noted a right eye cataract. Dr. Seewell has contacted your office asking for your opinion on discontinuing her aspirin and/or clopidogrel to reduce bleeding risk during her cataract surgery, which has been scheduled for next week. She feels the bleeding risk on both medications is too high to perform the surgery. You should call Dr. Seewell back and tell her:

A. "Discontinue aspirin, continue clopidogrel, and proceed with cataract surgery."
B. "Discontinue clopidogrel, continue aspirin, and proceed with cataract surgery."
C. "Discontinue both aspirin and clopidogrel and proceed with cataract surgery."
D. "Postpone the surgery for at least 6 months, and preferably 12 months, at which time the clopidogrel can be discontinued."
E. "I will advise Ms. Heyward to find an ophthalmologist who will perform the surgery while she is on both aspirin and clopidogrel as she will never be able to stop either medication."

IV-142. Which of the following features is associated with higher risk of complications during percutaneous coronary intervention?

A. Age >65 years
B. Emergent procedure
C. Chronic kidney disease
D. Cardiogenic shock
E. All of the above

IV-143. A 28-year-old woman has hypertension that is difficult to control. She was diagnosed at age 26. Since that time she has been on increasing amounts of medication. Her current regimen consists of labetalol 1000 mg bid, lisinopril 40 mg qd, clonidine 0.1 mg bid, and amlodipine 5 mg qd. On physical examination she appears to be without distress. Blood pressure is 168/100, and heart rate is 84 beats/min. Cardiac examination is unremarkable, without rubs, gallops, or murmurs. She has good peripheral pulses and has no edema. Her physical appearance does not reveal any hirsutism, fat maldistribution, or abnormalities of genitalia. Laboratory studies reveal a potassium of 2.8 mEq/dL and a serum bicarbonate of 32 mEq/dL. Fasting blood glucose is 114 mg/dL. Which of the following is the most likely diagnosis?

A. Congenital adrenal hyperplasia
B. Cushing syndrome
C. Conn syndrome
D. Fibromuscular dysplasia
E. Pheochromocytoma

IV-144. In the patient described in question IV-143, which of the following is the best way to diagnose her disease?

A. 24-Hour urine collection for cortisol
B. 24-Hour urine collection for metanephrines
C. MRI of the renal arteries
D. Plasma aldosterone/renin ratio
E. Renal vein renin levels

IV-145. Mr. Wilkins is brought to the emergency room by his wife for a worsening headache over the last day, and confusion starting about an hour ago. His blood pressure on presentation is 230/140 and heart rate is 90 beats/min. Arterial oxygen saturation is 95%. On examination, he is moving all extremities equally and there are no obvious deficits in his cranial nerve function, but he is clearly delirious. Cardiac examination reveals an enlarged and forceful point of maximal impulse and an S_4 gallop; his lungs are clear to auscultation. Laboratory studies show a creatinine of 2.4 mg/dL, 2+ protein in his urine with hematuria, and a hematocrit of 32% with normal platelet count. You examine his peripheral blood smear and notice schistocytes. Emergent brain MRI shows old microvascular changes but no acute infarct or hemorrhage. Regarding his blood pressure management, which of the following would be the most reasonable therapeutic course?

A. 0.1 mg of clonidine orally
B. 20 mg of oral lisinopril
C. 20 mg of IV labetalol and start a continuous parenteral drip for goal mean arterial pressure of 125 mmHg in the first hour
D. 90 mg of immediate-release oral nifedipine
E. Emergent plasmapheresis

IV-146. Which of the following statements regarding hypertension in African Americans is true?

A. Hypertension appears earlier in African Americans.
B. Hypertension is associated with higher morbidity and mortality in African Americans.
C. Hypertension is more severe in African Americans.
D. Hypertension is more prevalent in African Americans.
E. All of the above are true.

IV-147. A large proportion of blood pressure is determined by peripheral vascular resistance. Which of the following anatomic vascular structures contribute most to systemic peripheral vascular resistance?

A. Capillaries
B. Large arteries (e.g., aorta)
C. Large veins
D. Small arteries and arterioles
E. Venules

IV-148. Pheochromocytoma is associated with all of the following syndromes EXCEPT:

A. Liddle syndrome
B. Multiple endocrine neoplasia type 2A
C. Multiple endocrine neoplasia type 2B
D. Neurofibromatosis
E. von Hippel-Lindau syndrome

IV-149. Which of the following statements regarding renal artery stenosis (RAS) is true?

A. An abnormally reduced renal artery flow velocity by Doppler ultrasound is predictive of hemodynamically significant stenosis.
B. Early in the course of RAS elevated systemic renin levels are typical.
C. In the general population the presence of fibromuscular dysplasia causing RAS is rare (<1% prevalence).
D. Levels of renin activity observed in RAS are predictive of response to medical therapy.
E. Usually the first clinical presentation of renal stenosis due to fibromuscular dysplasia is reduced renal function.

IV-150. A 75-year-old man went for a diagnostic coronary angiography after an abnormal stress test. Arterial access was obtained easily in the right femoral artery, and the angiography completed with 35 cc of iodinated contrast dye. Fortunately, no significant coronary stenosis was noted. Seven days later, he returns to the emergency room with abdominal pain and nausea. He reports that his urine output has been poor recently. Examination reveals a slight fever (38.3°C) and livedo reticularis on his lower extremities. Laboratory studies show a creatinine of 2.7 mg/dL (previously was 1.1), white blood cell count of 10,500/mL with 21% eosinophils, and an erythrocyte sedimentation rate of 92 mm/h. Which of the following is the mostly likely diagnosis?

A. Acute interstitial nephritis
B. Atheroembolic renal disease
C. Churg-Strauss syndrome
D. Contrast-induced nephropathy
E. Hypereosinophilic syndrome

IV-151. You are in the emergency department when a 67-year-old woman is admitted with acute nausea, vomiting, and flank pain. She has a history of atrial fibrillation but has not been compliant with her oral anticoagulation. She is hypertensive to 220/140. Labs reveal an extreme elevation in lactic acid dehydrogenase and moderate leukocytosis. With a clinical suspicion as to the diagnosis, you order a CT angiogram, which is shown Figure IV-151. Which of the following is the diagnosis?

A. Cushing syndrome
B. Pheochromocytoma
C. Thrombotic renal infarction
D. Thrombotic thrombocytopenic purpura
E. Urinary tract infection

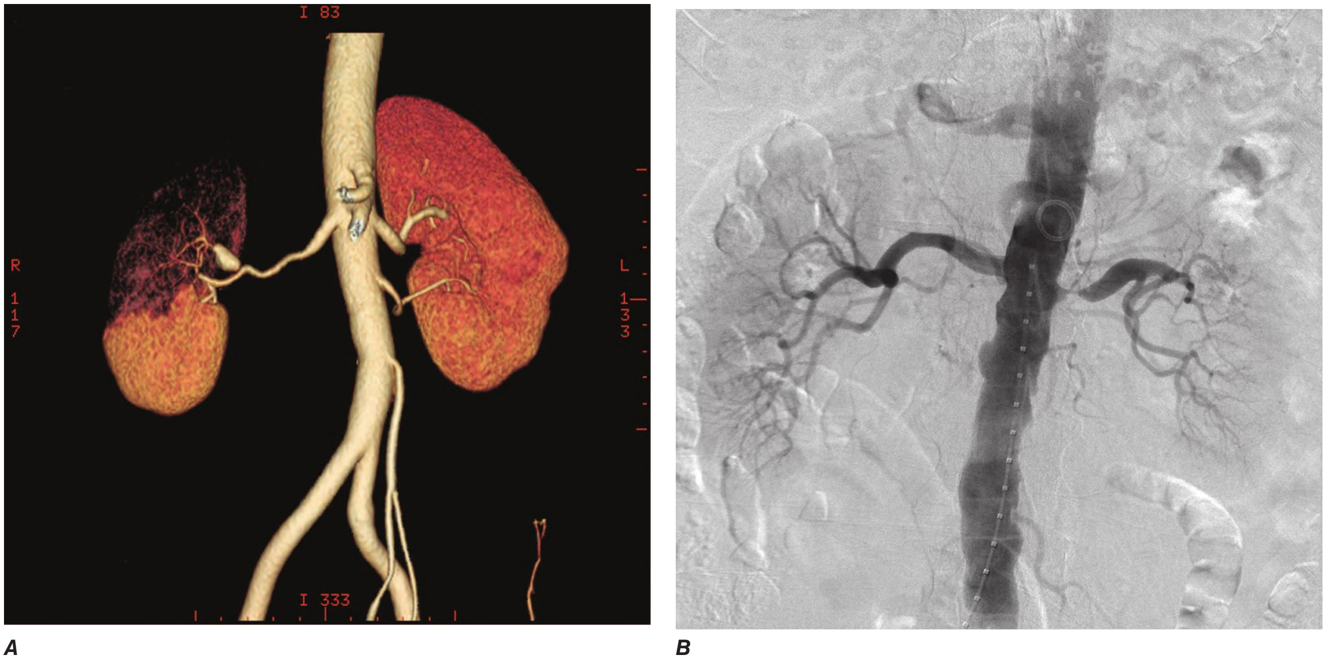


FIGURE IV-151

IV-152. In which of the following patients that present to an emergency department reporting acute dyspnea would a positive D-dimer result prompt additional testing for a pulmonary embolism?

A. A 24-year-old woman who is 32-weeks pregnant.
B. A 48-year-old man with no past medical history who presents with calf pain following prolonged air travel; the alveolar-arterial oxygen gradient is normal.
C. A 56-year-old woman undergoing chemotherapy for breast cancer.
D. A 62-year-old man who underwent hip replacement surgery 4 weeks previously.
E. A 72-year-old man who had an acute myocardial infarction 2 weeks ago.

IV-153. Which of the following statements regarding pulmonary embolism is true?

A. Airway resistance usually decreases in the setting of an acute pulmonary embolism.
B. Almost all patients with pulmonary embolism have evidence of deep vein thrombosis at the time.
C. Alveolar hyperventilation is a typical physiologic abnormality in the presence of pulmonary embolism.
D. Hypotension in the setting of acute pulmonary embolism is often due to acute left ventricular systolic dysfunction.
E. The size of the arterial-alveolar gradient is invariably correlated with the size of the pulmonary embolism.

IV-154. Ms. Tupulo is a 45-year-old woman with a history of morbid obesity (weight 140 kg), hypertension, and diabetes. She has been in the hospital for 4 days after having open surgical gastric bypass surgery. On postoperative day 4, she experiences sudden breathlessness, tachycardia, hypoxia, and an overwhelming sense of impending doom. Urgent chest CT angiography reveals a saddle pulmonary embolism. Her blood pressure is 70/45 and urine output is poor; 500cc of normal saline is administered IV and she is initiated on dobutamine 5 mcg/kg per minute with a subsequent blood pressure of 82/55. What is the next most appropriate step?

A. Enoxaparin
B. Inferior vena cava filter
C. Surgical pulmonary embolectomy
D. Tissue plasminogen activator
E. Urokinase

IV-155. You admit Mr. Casey, a 57-year-old traveling salesman, who was diagnosed with a pulmonary embolism (PE) in the emergency department. On arrival, his blood pressure was 127/83, arterial saturation was 97%, and respiratory rate mildly elevated at 16 breaths/min. He is dyspneic on exertion but feels okay at rest. On echocardiogram, his right ventricle is dilated and hypokinetic. Troponin I is mildly elevated as is his B-type natriuretic peptide. Which of the following classifications best describes Mr. Casey's PE?

A. Catastrophic
B. Low risk
C. Massive
D. Saddle
E. Submassive

IV-156. All of the following statements regarding deep vein thrombosis (DVT)/pulmonary embolism (PE) prophylaxis in the inpatient setting are true EXCEPT:

A. Computerized reminder systems are ineffective in increasing the use of effective DVT prophylaxis.
B. DVT is easily detected when present.
C. DVT/PE is rare enough to not pose a serious medical or economic burden.
D. Patients with a contraindication to anticoagulation require no DVT prophylaxis.
E. All of the above statements are FALSE.

IV-157. You are taking signout from your partner, Dr. Gneauxsalot, when he mentions that a patient has an arterial pseudoaneurysm. Which of the following differentiates a pseudoaneurysm from a true aneurysm?

A. A pseudoaneurysm is a radiologic artifact, whereas a true aneurysm is physically present.
B. A pseudoaneurysm is the same as a true aneurysm.
C. In a pseudoaneurysm, the intima and media are disrupted and the dilated segment of the artery is lined by the adventitia only. In an aneurysm, all three layers are intact.
D. Pseudoaneurysms are a perceived dilation that is present before or after arterial bifurcations, whereas true aneurysms occur anatomically separate from arterial bifurcations.
E. Pseudoaneurysms pose no danger to the patient, whereas true aneurysm carries risk of rupture.

IV-158. You are assessing a patient who was found to have an aortic aneurysm on CT scan of her chest. You note she has hypertelorism (widely spaced eyes), a bifid uvula, and on CT of the neck has "corkscrew" carotids. You suspect Loeys-Dietz syndrome. A gene mutation for which of the following proteins is responsible for the Loeys-Dietz syndrome?

A. Cystic fibrosis transmembrane conductance regulator
B. Fibrillin-1
C. STK11 gene
D. Transforming growth factor-β receptor
E. Type III procollagen

IV-159. Which of the following rheumatologic diseases is associated with a risk for aortic aneurysms?

A. Ankylosing spondylitis
B. Psoriatic arthritis
C. Reactive arthritis (formerly known as Reiter syndrome)
D. Rheumatoid arthritis
E. All of the above

IV-160. In thoracic aortic aneurysms, which of the following factors is most strongly associated with future risk of aneurysm rupture?

A. Patient age
B. Patient height
C. Patient weight
D. Diameter of the aneurysm
E. Time duration from diagnosis

IV-161. You are a cardiothoracic surgeon asked to see Mr. Schulley, a 55-year-old man with a known bicuspid aortic valve. He has developed symptomatic aortic stenosis and requires aortic valve replacement. Coronary angiogram shows no coronary artery disease and echocardiogram shows that the remaining three cardiac valves function normally. Assessment of what other cardiovascular structure is required for operative planning?

A. Inferior vena cava
B. Pulmonary artery
C. Renal arteries
D. Superior vena cava
E. Thoracic aorta

IV-162. Mr. Tomazelli is a 75-year-old man with diabetes mellitus and hypertension. Despite continued counseling he has been unable to stop smoking imported unfiltered cigarettes. At your visit today, he complains of burning pain in his bilateral calves with ambulation. It typically occurs after about two city blocks of walking on flat ground and improves with rest. He has also noted some aching calf pain during the night that improves when he sits on the side of the bed. Which of the following is likely true for Mr. Tomazelli?

A. He likely has critical aorto-iliac arterial stenosis.
B. The amplitude of his pulse volume contour will be sharp and spiked.
C. The most likely etiology of his symptoms is femoral arterial fibromuscular dysplasia.
D. The next most-reasonable diagnostic test is magnetic resonance angiography.
E. The ratio of the systolic blood pressure in his ankle versus his brachial artery is likely less than 0.9.

IV-163. A 32-year-old construction foreman presents with exertional pain in his bilateral forearms and hands. He smokes 1 pack per day of cigarettes; otherwise, has no past medical history. He has an easily palpable brachial pulse but very faint radial and ulnar pulses. Angiography of his upper extremity reveals smooth tapering segmental lesions in the small distal arterial vessels. Which of the following treatments has the greatest chance of success?

A. Cilostazol
B. Enoxaparin
C. Prednisone
D. Smoking cessation
E. Warfarin

IV-164. Mr. Bumgartner is a 22-year-old right-handed college baseball player. Over the past month, he has noticed that after throwing the baseball repeatedly he gets significant muscle pain in his right arm. Raising his arm up above his head or really doing much with it will cause claudication-like pain. In the clinic, you ask him to abduct his right arm and externally rotate the shoulder, which immediately recreates his symptoms. You suspect which of the following?

A. Aortic stenosis
B. Cervical epidural abscess
C. Coarctation of the aorta
D. Strained bicep muscle
E. Thoracic outlet compression syndrome

IV-165. Mr. Velazques is a 24-year-old man you are seeing for dyspnea. When he was 7 years old he fell while climbing a fence and suffered a stab wound to his left arm. On examination, you note that there is a pulsatile mass at the site of the stab wound. Auscultation over this mass reveals a loud bruit. When you compress the mass, his heart rate slows from 95 to 75 beats/min. In evaluation of his dyspnea, he has signs of congestive heart failure, echocardiogram reveals cardiomegaly, and chest x-ray shows mild pulmonary edema. What therapy will likely cure the patient?

A. Six months of penicillin
B. Initiation of lisinopril, metoprolol, and spironolactone
C. Heart transplant
D. Mitral valve replacement
E. Surgical excision of the lesion causing the pulsatile mass

IV-166. Which of the statements regarding chronic venous disease is true?

A. More men than women suffer from varicose veins.
B. More men than women suffer from chronic venous insufficiency with edema.
C. More than 50% of patients over 70 years old have chronic venous insufficiency.
D. Most patients with chronic venous insufficiency will develop venous ulcers.
E. All of the above are true.

IV-167. You are taking care of a patient who suffers from chronic lymphedema due to recurrent streptococcal lymphangitis as a child. She finds her leg swelling unsightly and asks about therapeutic options. All of the following are reasonable therapeutic options for chronic lymphedema EXCEPT:

A. Decongestive physiotherapy
B. Diuretic therapy
C. Frequent leg elevation
D. Intermittent pneumatic compression devices
E. Liposuction

IV-168. All of the following are appropriate therapeutic steps for varicose veins EXCEPT:

A. Aspirin.
B. Avoid prolonged standing.
C. Frequent elevation of the lower extremities.
D. Graduated compression stockings.
E. All of the above are appropriate.

IV-169. Which of the following tests is the gold standard for the diagnosis of pulmonary hypertension and to guide medical therapeutic options?

A. CT chest with and without IV contrast
B. Echocardiogram
C. Pulmonary function tests
D. Right heart catheterization
E. Ventilation/perfusion scan

IV-170. You perform a right heart catheterization with vasodilator testing (using inhaled nitric oxide) on a patient with known idiopathic pulmonary arterial hypertension. The hemodynamics are listed below.

	Baseline	With Inhaled Nitric Oxide
Pulmonary artery pressure (mmHg)	90/50 (65)	45/20 (28)
Pulmonary capillary wedge pressure (mmHg)	6	8
Cardiac output (L/min)	4.2	5.2
Pulmonary vascular resistance (Wood units)	14	3.8

Based on these data, which is the best therapy for this patient?

A. Bosentan
B. Epoprostenol
C. Lung transplant
D. Diltiazem
E. Sildenafil

IV-171. Mr. Rhodes is a 45-year-old man who presented to his primary care physician with 4 months of worsening dyspnea. Pulmonary function tests and CT chest are normal. Echocardiogram shows elevated right ventricular systolic pressure estimates by Doppler velocities and left ventricular diastolic dysfunction with normal systolic function. Based on this information he undergoes a right heart catheterization. Hemodynamics are shown below.

Right atrium	10 mmHg
Pulmonary artery	55/35 (42) mmHg
Pulmonary capillary wedge pressure	34 mmHg
Left ventricular end-diastolic pressure	34 mmHg
Cardiac output	4.5 L/min
Pulmonary vascular resistance	1.8 Wood unit

Which of the following is the most likely cause of Mr. Rhodes' pulmonary hypertension?

A. Chronic lung disease
B. Chronic thromboembolic pulmonary hypertension
C. Heart failure with preserved ejection fraction
D. Idiopathic pulmonary arterial hypertension
E. Mitral stenosis

ANSWERS

IV-1. **The answer is C.** *(Chap. 231)* While age-adjusted death rates for coronary heart disease have declined by two-thirds in the last four decades in the United States, cardiovascular diseases remain the most common causes of death, responsible for 35% of all deaths, almost 1 million deaths each year. Approximately one-fourth of these deaths are sudden. In addition, cardiovascular diseases are highly prevalent, diagnosed in 80 million adults, or ~35% of the adult population. The growing prevalence of obesity, type 2 diabetes mellitus, and metabolic syndrome threatens to reverse the progress that has been made in the age-adjusted reduction in the mortality rate of coronary heart disease.

IV-2. **The answer is D.** *(Chap. 231)* For years, cardiovascular disease was thought to be more common in men than in women. However, while the absolute number of deaths secondary to cardiovascular disease has declined over the past decades in men, this number has actually risen in women. In fact, the percentage of all deaths secondary to cardiovascular disease is higher among women (43%) than among men (37%) In addition, Inflammation, obesity, type 2 diabetes mellitus, and the metabolic syndrome appear to play more prominent roles in the development of coronary atherosclerosis in women than in men. Coronary artery disease is more frequently associated with dysfunction of the coronary microcirculation in women than in men. Exercise electrocardiography has a lower diagnostic accuracy in the prediction of epicardial obstruction in women than in men.

IV-3. **The answer is D.** *(Chap. 231)* The majority of heart murmurs are midsystolic and soft (grades I–II/VI). When such a murmur occurs in an asymptomatic child or young adult without other evidence of heart disease on clinical examination, it is usually benign and echocardiography generally is not required (Figure IV-3). In contrast, two-dimensional and Doppler echocardiography are indicated in patients with loud systolic murmurs (grades ≥III/VI), especially those that are holosystolic or late systolic, and in patients with diastolic or continuous murmurs.

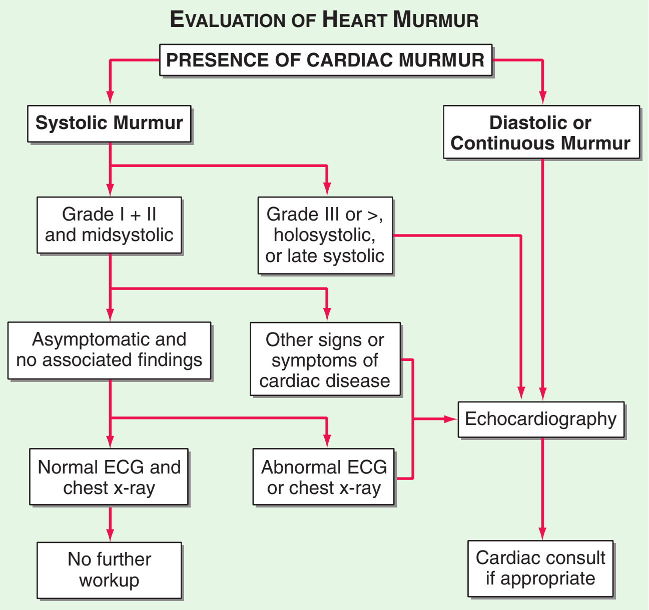

EVALUATION OF HEART MURMUR
PRESENCE OF CARDIAC MURMUR
Systolic Murmur
Diastolic or Continuous Murmur
Grade I + II and midsystolic
Grade III or >, holosystolic, or late systolic
Asymptomatic and no associated findings
Other signs or symptoms of cardiac disease
Echocardiography
Normal ECG and chest x-ray
Abnormal ECG or chest x-ray
No further workup
Cardiac consult if appropriate

FIGURE IV-3 ***Abbreviation:*** ECG, electrocardiogram. Reproduced with permission from Braunwald E et al: *Primary Cardiology*, 2nd ed. Philadelphia: Saunders, 2003.

IV-4. **The answer is A.** *(Chap. 232)* The sliding filament model for muscle contraction rests on the central observation that both the thick and the thin filaments are constant in length during both contraction and relaxation. With activation, the actin filaments are propelled farther into the A band. In the process, the A band remains constant in length, whereas the I band shortens and the Z lines move toward one another. The sarcomere, the structural and functional unit of contraction, lies between adjacent Z lines, which are dark repeating bands apparent on transmission electron microscopy. The distance between Z lines varies with the degree of contraction or stretch of the muscle and ranges between 1.6 and 2.2 μm. At the center of the sarcomere is a dark band of constant length (1.5 μm), the A band, which is flanked by two lighter bands, the I bands, which are of variable length. The sarcomere of heart muscle, like that of skeletal muscle, consists of interdigitating thick and thin myofilaments. Thicker filaments, composed principally of the protein myosin, traverse the A band; they are about 10 nm (100 Å) in diameter, with tapered ends. Thinner filaments, composed primarily of actin, course from the Z lines through the I band into the A band; they are ~5 nm (50 Å) in diameter and 1.0 μm in length. Thus, thick and thin filaments overlap only within the (dark) A band, whereas the (light) I band contains only thin filaments. On electron-microscopic examination, bridges extend between the thick and thin filaments within the A band; these are myosin heads (Figure IV-4) bound to actin filaments.

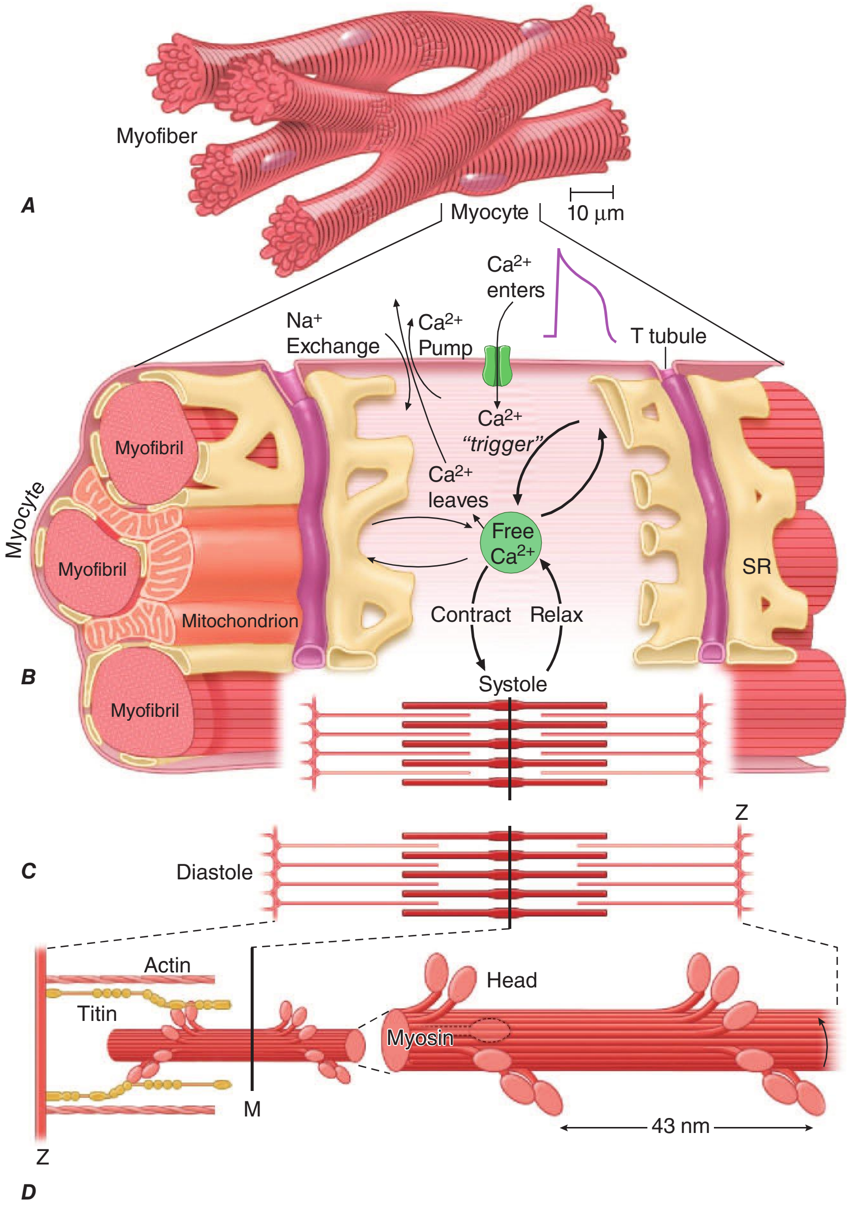

Myofiber
A
Myocyte
10 μm
Ca2+ enters
Na+ Exchange
Ca2+ Pump
T tubule
Ca2+ "trigger"
Ca2+ leaves
Myofibril
Myocyte
Free Ca2+
Myofibril
SR
Mitochondrion
Contract
Relax
B
Systole
Myofibril
Z
C
Diastole
Actin
Head
Titin
Myosin
M
43 nm
Z
D

FIGURE IV-4 Reproduced with permission from Opie LH: *Heart Physiology: From Cell to Circulation*, 4th ed. Philadelphia: Lippincott, Williams & Wilkins, 2004.

IV-5. **The answer is A.** *(Chap. 232)* During activation of the cardiac myocyte, Ca^{2+} binds the heterotrimer troponin C, resulting in conformational changes in the regulatory protein tropomyosin and exposing actin cross-bridge interaction sites (Figure IV-5). Repetitive interaction between myosin heads and actin filaments is termed cross-bridge cycling, and results in sliding of the actin along the myosin filaments, with muscle shortening and/or the development of tension. The splitting of adenosine triphosphate (ATP) then dissociates the myosin cross-bridge from actin. In the presence of ATP, actin and myosin filaments bind and dissociate cyclically if sufficient Ca^{2+} is present; these linkages cease when [Ca^{2+}] falls below a critical level, and the troponin-tropomyosin complex once more inhibits actin-myosin interactions. Intracytoplasmic [Ca^{2+}] is the principal determinant of the inotropic state of the heart. Most agents that stimulate myocardial contractility (positive inotropic stimuli), including digitalis glycosides and β-adrenergic agonists, increase cytoplasmic [Ca^{2+}], triggering cross-bridge cycling. Increased adrenergic neuronal activity stimulates myocardial contractility through norepinephrine release, activation of β adrenergic receptors, and, via Gs-stimulated guanine nucleotide-binding proteins, activation of the adenylyl cyclase, which leads to the formation of the intracellular second messenger cyclic adenosine monophosphate (AMP) from ATP. Cyclic AMP in turn activates protein kinase A, which phosphorylates sarcolemmal Ca^{2+} channels, enhancing the influx of Ca^{2+} into the myocyte.

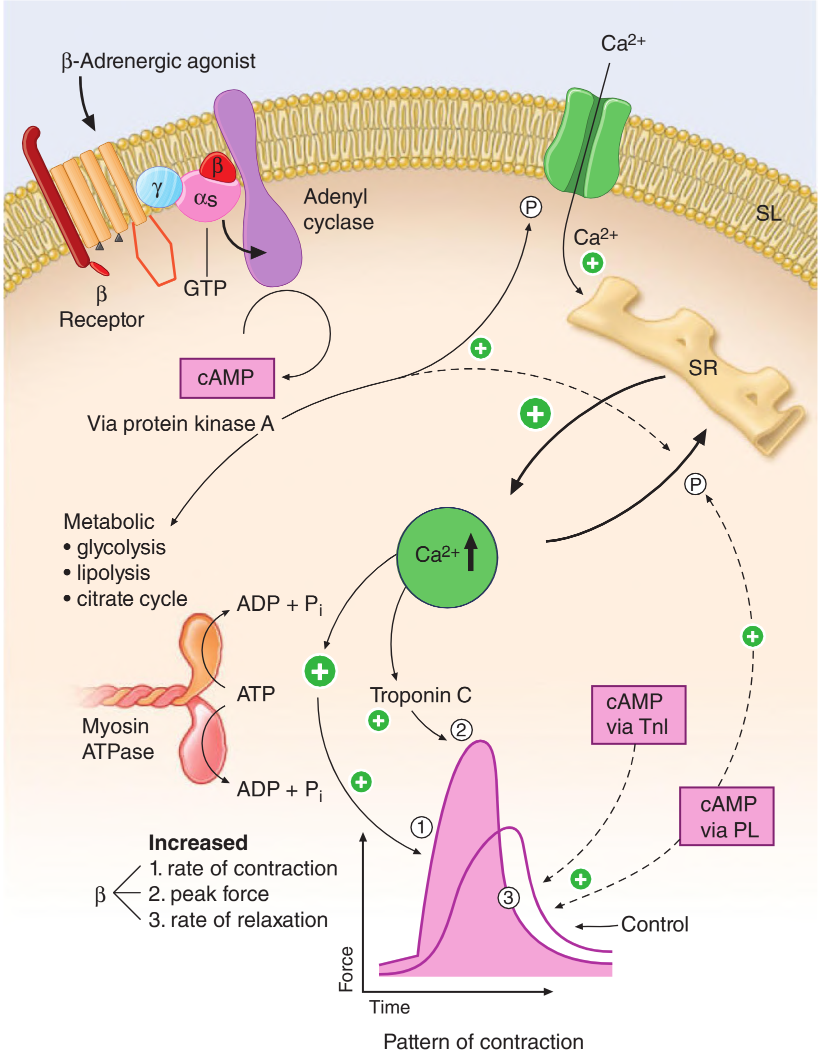

β-Adrenergic agonist
Ca2+
γ
β
αs
Adenyl cyclase
Ⓟ
Ca2+
SL
β Receptor
GTP
cAMP
SR
Via protein kinase A
Ⓟ
Metabolic
• glycolysis
• lipolysis
• citrate cycle
Ca2+
ADP + Pi
ATP
Myosin ATPase
ADP + Pi
Troponin C
②
cAMP via TnI
cAMP via PL
①
③
Increased
β
1. rate of contraction
2. peak force
3. rate of relaxation
Control
Force
Time
Pattern of contraction

FIGURE IV-5 Reproduced with permission from Opie LH: *Heart Physiology: From Cell to Circulation*, 4th ed. Philadelphia: Lippincott, Williams & Wilkins, 2004.

IV-6. **The answer is C.** *(Chap. 233)* The global rise in cardiovascular disease (CVD) is the result of an unprecedented transformation in the causes of morbidity and mortality during the 20th century. Known as the epidemiologic transition, this shift is driven by industrialization, urbanization, and associated lifestyle changes and is taking place in every part of the world among all races, ethnic groups, and cultures. The transition is divided into four basic stages: pestilence and famine, receding pandemics, degenerative and man-made diseases, and delayed degenerative diseases. A fifth stage, characterized by an epidemic of inactivity and obesity, is emerging in some countries. The stages of the epidemiologic transition are shown in Table IV-6.

TABLE IV-6 Five Stages of the Epidemiologic Transition

Stage	Description	Deaths Related to CVD, %	Predominant CVD Type
Pestilence and famine	Predominance of malnutrition and infectious diseases as causes of death; high rates of infant and child mortality; low mean life expectancy	<10	Rheumatic heart disease, cardiomyopathies caused by infection and malnutrition
Receding pandemics	Improvements in nutrition and public health lead to decrease in rates of deaths related to malnutrition and infection; precipitous decline in infant and child mortality rates	10–35	Rheumatic valvular disease, hypertension, CHD, and stroke (predominantly hemorrhagic)
Degenerative and man-made diseases	Increased fat and caloric intake and decrease in physical activity lead to emergence of hypertension and atherosclerosis; with increase in life expectancy, mortality from chronic, noncommunicable diseases exceeds mortality from malnutrition and infectious disease	35–65	CHD and stroke (ischemic and hemorrhagic)
Delayed degenerative diseases	CVD and cancer are the major causes of morbidity and mortality; better treatment and prevention efforts help avoid deaths among those with disease and delay primary events; age-adjusted CVD morality declines; CVD affecting older and older individuals	40–50	CHD, stroke, and congestive heart failure
Inactivity and obesity	Overweight and obesity increase at alarming rate; diabetes and hypertension increase; decline in smoking rates levels off; a minority of the population meets physical activity recommendations	38	CHD, stroke, and congestive heart failure, peripheral vascular disease

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease.
Source: Data from Omran AR: The epidemiologic transition: a theory of the epidemiology of population change. *Milbank Mem Fund Q* 49:509, 1971 and Olshansky SJ et al: The fourth stage of the epidemiologic transition: the age of delayed degenerative diseases. *Milbank Q* 64:355, 1986.

Note that CVD mortality peaks in the third stage, and then tends to decline aided by preventive strategies such as smoking cessation programs and effective blood pressure control, acute hospital management, and technological advances, such as the availability of bypass surgery. In the stage of receding pandemics, the majority of CVD risk tends to be due to coronary heart disease, stroke, and rheumatic heart disease. Typically, the rate of CHD deaths exceeds that of stroke by a ratio of 2:1 to 3:1. While the stages of epidemiologic transition is a useful construct to generalize expectations regarding CVD epidemiology over time, every nation experiences these stages in unique fashion due to different environmental, behavioral, and genetic differences.

IV-7. **The answer is C.** *(Chap. 234)* This patient has classic findings of differential cyanosis, or isolated cyanosis (and clubbing in this case) of the lower, but not upper extremities. This limits the differential diagnosis to only one possibility—patient ductus arteriosus with secondary pulmonary hypertension causing right-to-left shunting at the level of the great vessels, distal to the upper extremity branches. Tetralogy of Fallot often causes central cyanosis due to right-to-left intracardiac shunting with no differential between the upper and lower extremities. Ventricular septal defect and arterial septal defect (ASD) often have no cyanosis evident as they are most often left-to-right shunts (unless pulmonary hypertension develops resulting in Eisenmenger syndrome). Transposition of great arteries may exhibit varying degrees of central cyanosis, depending on the intracardiac anatomy (most often present with an ASD).

IV-8. **The answer is E.** *(Chap. 234)* Jugular venous pulse (JVP) is the single most important bedside measurement from which to estimate the volume status. The internal jugular vein is preferred because the external jugular vein is valved and not directly in line with the superior vena cava and right atrium. Precise estimation of the central venous or right atrial pressure from bedside assessment of the jugular venous waveform has proved difficult. Venous pressure traditionally has been measured as the vertical distance between the top of the jugular venous pulsation and the sternal inflection point (angle of Louis). A distance >4.5 cm at 30° elevation is considered abnormal. However, the actual distance between the mid-right atrium and the angle of Louis varies considerably as a function of both body size and the patient angle at which the assessment is made (30°, 45°, or 60°). The use of the sternal angle as a reference point leads to systematic underestimation of central venous pressure (CVP), and this method should be used less for semi-quantification than to distinguish a normal from an abnormally elevated CVP. Venous pulsations above this level in the sitting position are clearly abnormal, as the distance between the clavicle and the right atrium is at least 10 cm.

Normally, the venous pressure should fall by at least 3 mmHg with inspiration. Kussmaul sign is defined by either a rise or a lack of fall of the JVP with inspiration and is classically associated with constrictive pericarditis, although it has been reported in patients with restrictive cardiomyopathy, massive pulmonary embolism, right ventricular infarction, and advanced left ventricular systolic heart failure. It is also a common, isolated finding in patients after cardiac surgery without other hemodynamic abnormalities.

IV-9. **The answer is A.** *(Chap. 234)* The length and width of the blood pressure cuff bladder should be 80 and 40% of the arm's circumference, respectively. A common source of error in practice is to use an inappropriately small cuff, resulting in marked overestimation of true blood pressure, or an inappropriately large cuff, resulting in underestimation of true blood pressure. The cuff should be inflated to 30 mmHg above the expected systolic pressure and the pressure released at a rate of 2–3 mmHg/s. Systolic and diastolic pressures are defined by the first and fifth Korotkoff sounds, respectively.

Very low (even 0 mmHg) diastolic blood pressures may be recorded in patients with chronic, severe atrial regurgitation (AR) or a large arteriovenous fistula because of enhanced diastolic "runoff." In these instances, both the phase IV and phase V Korotkoff sounds should be recorded. Blood pressure is best assessed at the brachial artery level, though it can be measured at the radial, popliteal, or pedal pulse level. In general, systolic pressure increases and diastolic pressure decreases when measured in more distal arteries.

Blood pressure should be measured in both arms, and the difference should be less than 10 mmHg. A blood pressure differential that exceeds this threshold may be associated with atherosclerotic or inflammatory subclavian artery disease, supravalvular aortic stenosis, aortic coarctation, or aortic dissection. Systolic leg pressures are usually as much as 20 mmHg higher than systolic arm pressures.

Greater leg–arm pressure differences are seen in patients with chronic severe AR as well as patients with extensive and calcified lower extremity peripheral arterial disease. The ankle-brachial index (lower pressure in the dorsalis pedis or posterior tibial artery divided by the higher of the two brachial artery pressures) is a powerful predictor of long-term cardiovascular mortality. The blood pressure measured in an office or hospital setting may not accurately reflect the pressure in other venues. "White coat hypertension" is defined by at least three separate clinic-based measurements >140/90 mmHg and at least two non-clinic-based measurements >140/90 mmHg in the absence of any evidence of target organ damage. Individuals with white coat hypertension may not benefit from drug therapy.

IV-10. **The answer is E.** *(Chap. 234)* Mr. Kobishigawa has evidence of pulsus alternans. Pulsus alternans is defined by beat-to-beat variability of pulse amplitude. It is present only when every other phase I Korotkoff sound is audible as the cuff pressure is lowered slowly, typically in a patient with a regular heart rhythm and independent of the respiratory cycle. Pulsus alternans is seen in patients with severe left ventricular systolic dysfunction and is thought to be due to cyclic changes in intracellular calcium and action potential duration. When pulsus alternans is associated with electrocardiographic T wave alternans, the risk for an arrhythmic event appears to be increased. Cardiac tamponade or large pericardial effusions can be associated with electrical alternans (a regular variability in the QRS voltage or vector) or pulsus paradoxus, a difference between the systolic pressure at which the Korotkoff sounds are first heard (during expiration) and the systolic pressure at which the Korotkoff sounds are heard with each heartbeat, independent of the respiratory phase. This is an exaggerated consequence of interventricular dependence. Atrial fibrillation would result in beat-to-beat variability of the pulse amplitude and an irregularly irregular rhythm.

IV-11. **The answer is A.** *(Chap. 234)* The murmur of hypertrophic obstructive cardiomyopathy (HOCM) has features of both obstruction to left ventricular (LV) outflow and mitral regurgitation, as would be expected from knowledge of the pathophysiology of this condition. The systolic murmur of HOCM usually can be distinguished from other causes on the basis of its response to bedside maneuvers, including Valsalva, passive leg raising, and standing/squatting. In general, maneuvers that decrease LV preload (or increase LV contractility) will cause the murmur to intensify, whereas maneuvers that increase LV preload or afterload will cause a decrease in the intensity of the murmur. Accordingly, the systolic murmur of HOCM becomes louder during the strain phase of the Valsalva maneuver and after standing quickly from a squatting position. The murmur becomes softer with passive leg raising and when squatting.

IV-12. **The answer is B.** *(Chap. 234)* The depolarization stimulus for the normal heartbeat originates in the sinoatrial node, or sinus node, a collection of pacemaker cells. These cells fire spontaneously; that is, they exhibit automaticity. Other cells exhibit automaticity, though at a slower rate, including atrioventricular (AV) nodal (junctional) cells and the Purkinje fiber cells. The first phase of cardiac electrical activation is the spread of the depolarization wave through the right and left atria, followed by atrial contraction. Next, the impulse stimulates pacemaker and specialized conduction tissues in the AV nodal and His-bundle areas; together, these two regions constitute the AV junction. The bundle of His bifurcates into two main branches, the right and left bundles, which rapidly transmit depolarization wavefronts to the right and left ventricular myocardium by way of Purkinje fibers. The main left bundle bifurcates into two primary subdivisions, a left anterior fascicle and a left posterior fascicle. The depolarization wavefronts then spread through the ventricular wall, from endocardium to epicardium, triggering ventricular contraction.

IV-13. **The answer is A.** *(Chap. 235)* The electrocardiogram waveforms are labeled alphabetically, beginning with the P wave, which represents atrial depolarization (Figure IV-13). The QRS complex represents ventricular depolarization, and the ST-T-U complex (ST segment, T wave, and U wave) represents ventricular repolarization. The J point is the junction between the end of the QRS complex and the beginning of the ST segment. Atrial repolarization (STa and Ta) is usually too low in amplitude to be detected, but it may become apparent in conditions such as acute pericarditis and atrial infarction.

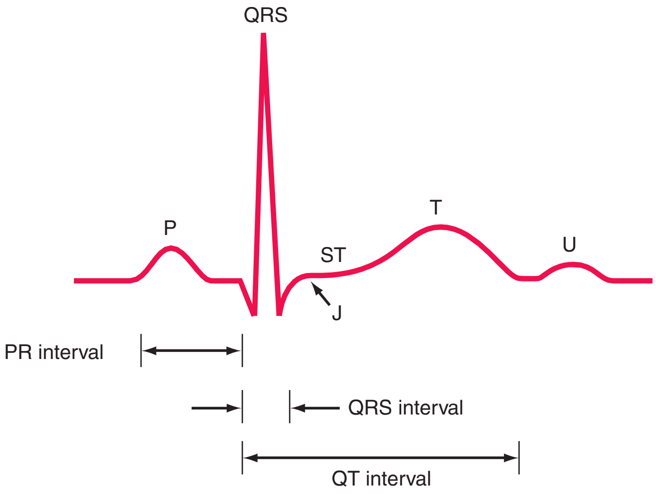


FIGURE IV-13

IV-14. **The answer is A.** *(Chap. 235).* Figure IV-14 depicts the limb leads and respective frontal plane axis categories on the electrocardiogram. Note that the normal axis extends from −30 to 90 or 100°.

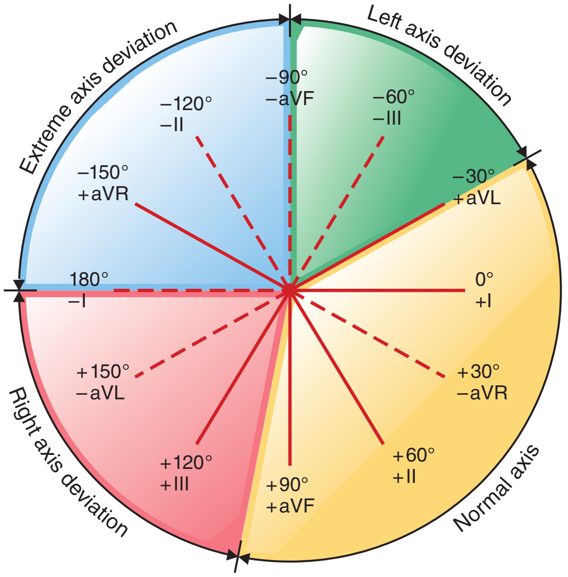


FIGURE IV-14

IV-15. **The answer is D.** *(Chap. 235)* From a clinical viewpoint, the division of acute myocardial infarction/ischemia into ST-segment elevation and non-ST elevation types is useful since the consistent efficacy of emergency (minutes to hours) reperfusion therapy is limited to the former group; the evolving indications for acute reperfusion therapy in non-ST elevation myocardial infarction are a focus of intensive investigation. The electrocardiogram leads are usually more helpful in localizing regions of ST elevation than non-ST elevation ischemia. For example, acute transmural anterior (including apical and lateral) wall ischemia is reflected by ST elevations or increased T wave positivity in one or more of the precordial leads (V_1–V_6) and leads I and aVL. Inferior wall ischemia produces changes in leads II, III, and aVF. “Posterior” wall ischemia (usually associated with lateral or inferior involvement) may be indirectly recognized by reciprocal ST depressions in leads V_1–V_3 (thus constituting an ST elevation “equivalent” acute coronary syndrome). Right ventricular ischemia usually produces ST elevations in right-sided chest leads. When ischemic ST elevations occur as the earliest sign of acute infarction, they typically are followed within a period ranging from hours to days by evolving T wave inversions and often by Q waves occurring in the same lead distribution.

IV-16. **The answer is B.** *(Chap. 235)* This is a classic presentation of worsening hyperkalemia and its recognition is crucial to facilitate early, life-saving treatment. In this case, the hyperkalemia was due to missed hemodialysis sessions. The earliest electrocardiogram (ECG) change with hyperkalemia is usually peaking (“tenting”) of the T waves. With further increases in the serum potassium concentration, the QRS complexes widen, the P waves decrease in amplitude and may disappear, and finally a sine wave pattern leads to asystole unless emergency therapy is given. As shown in Figure IV-16B, hypokalemia may cause “U” waves. Hypocalcemia causes a prolongation of the QT interval, and hypercalcemia may cause shortening of the QT interval. Derangements in sodium concentration usually do not cause apparent ECG abnormalities.

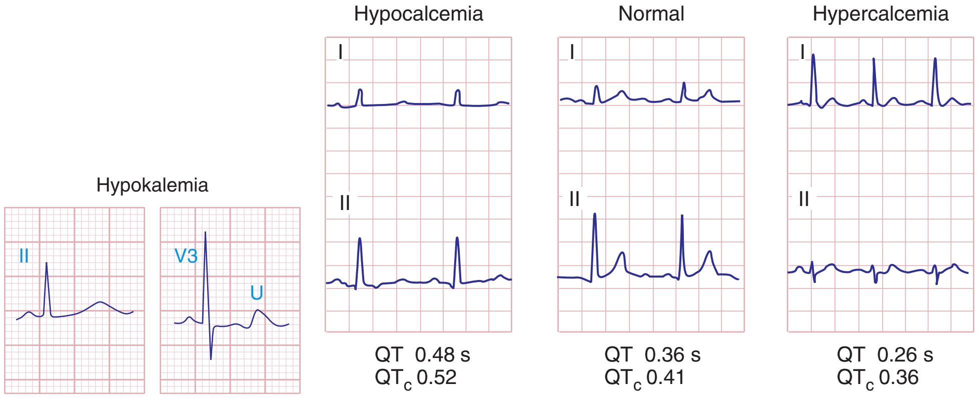


FIGURE IV-16B

IV-17. **The answer is D.** *(Chap. 235)* The electrocardiogram (ECG) (see Figure IV-17) is a classic triad indicating pericardial effusion, often with tamponade. Low voltage, sinus tachycardia, and electrical alternans are best seen in leads V_3 and V_4. This triad is highly specific for pericardial effusion, usually with tamponade physiology, but it is of limited sensitivity. Although chronic obstructive pulmonary disease exacerbation and myocardial amyloidosis can cause low ECG voltage, they are not associated with electrical alternans, and the former is usually not associated with hypotension unless acidosis or hypoxia is severe. Anterior myocardial infarction is hallmarked by ST elevation in V_1–V_3 and often I and aVL. The ECG in pulmonary embolism may demonstrate the McGinn-White sign, of S1Q3T3 (prominent S wave in lead I, with Q waves and T wave inversion in lead III). However, these ECG findings in acute pulmonary embolism are neither sensitive nor specific.

IV-18. **The answer is B.** *(Chap. 236)* Table IV-18 summarizes the relative diagnostic accuracies of cardiac imaging modalities for the diagnosis of coronary artery disease.

TABLE IV-18 **Comparative Diagnostic Accuracy of Cardiac Imaging Approaches to Coronary Artery Disease**

Imaging Modality	Published Data	Sensitivity (%)	Specificity (%)
Exercise echocardiography	15 studies (n = 1849 patients)	84	82
Dobutamine echocardiography	28 studies (n = 2246 patients)	80	84
SPECT MPI	113 studies (n = 11,212 patients)	88	76
Myocardial perfusion PET	9 studies (n = 650 patients)	93	81
CMR perfusion	37 studies (n = 2841 patients)	91	81
CMR wall motion	14 studies (n = 754 patients)	83	86
Coronary CTA	18 studies (n = 1286 patients)	99	89

Note: In these studies, the diagnosis of coronary artery disease was based on the presence of a >50% or >70% stenosis on invasive coronary angiography.

Abbreviations: CMR, cardiac magnetic resonance; CTA, computed tomography angiography; MPI, myocardial perfusion imaging; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

IV-19. **The answer is A.** *(Chap. 236)* Single-photon emission CT myocardial perfusion imaging is the most common form of stress imaging tests for coronary artery disease evaluation. The presence of a reversible myocardial perfusion defect as seen here is indicative of ischemia. Here, there is a reversible defect in the anterior and anteroseptal walls (arrows), reflecting significant obstructive disease in the left anterior descending coronary artery, which was subsequently confirmed on angiography (Figure IV-19B). A lesion in the left main coronary artery would likely demonstrate more extensive left ventricular defects since it supplies both the left anterior descending and left circumflex coronary arteries. A lesion in the left circumflex would typically demonstrate defects in the lateral and posterior left ventricle walls. A defect in the right coronary artery would typically demonstrate defects in the right ventricle and the base of the left ventricle.

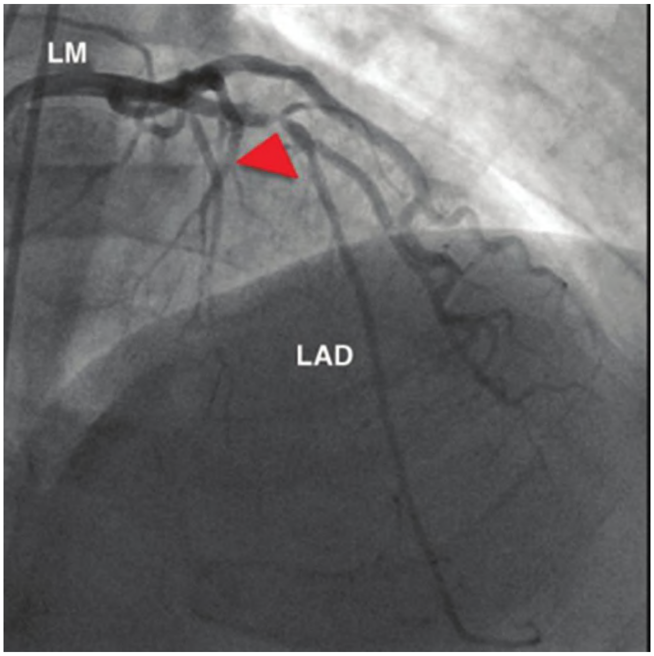


FIGURE IV-19B *Abbreviations:* LAD, left anterior descending artery; LM, left main coronary artery.

IV-20. **The answer is E.** *(Chap. 237)* Atrial pressure tracings have a characteristic "a" wave that reflects atrial contraction and a "v" wave that reflects pressure changes in the atrium during ventricular systole. Ventricular pressure tracings have a low-pressure diastolic filling period and a sharp rise in pressure that occurs during ventricular systole. When the catheter traverses the pulmonic valve from the right ventricle into the pulmonary artery, the diastolic pressure rises and the systolic pressure remains relatively unchanged. The pulmonary capillary wedge pressure is meant to reflect the left atrial pressure and should be less than the pulmonary artery diastolic pressure (Figure IV-20B).

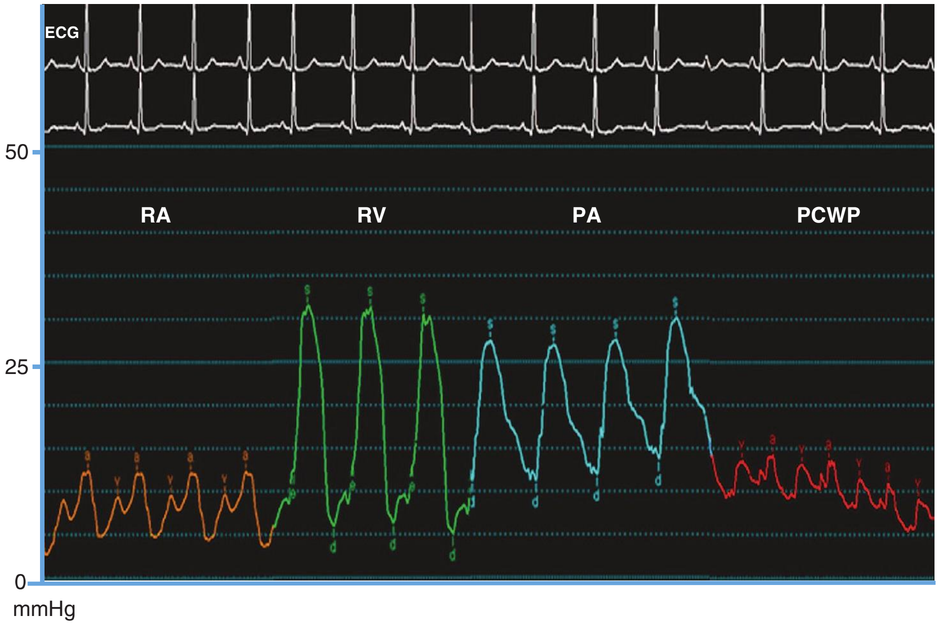


FIGURE IV-20B *Abbreviations:* PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; RA, right atrium; RV, right ventricle.

IV-21. The answer is A. *(Chap. 237)* This patient has a "step-up" in oxygen saturations between the vena cavae and the right atrium, indicative of a shunting of oxygenated blood from the left heart to the right atrium. This occurs with an atrial septal defect. The small increase in oxygen from the superior vena cava to inferior vena cava is expected and due to reduced oxygen extraction by the kidneys relative to other vascular beds. A ventricular septal defect with left-to-right shunting should present with a saturation step-up in the right ventricle. Right-to-left shunting causes systemic hypoxemia and cannot be confirmed by serial oximetry during right heart catheterization alone, and it requires either left heart catheterization or advanced imaging. Patent ductus arteriosus (PDA) would cause an oxygenation step-up at the level of the pulmonary artery as oxygenated blood flows from the aorta to the pulmonary artery through the PDA.

IV-22. The answer is A. *(Chap. 238)* The normal cardiac impulse is generated by pacemaker cells in the sinoatrial node situated at the junction of the right atrium and the superior vena cava. This impulse is transmitted slowly through nodal tissue to the anatomically complex atria, where it is conducted more rapidly to the atrioventricular node (AVN), inscribing the P wave of the electrocardiogram (ECG). There is a perceptible delay in conduction through the anatomically and functionally heterogeneous AVN. The time needed for activation of the atria and the AVN delay is represented as the PR interval of the ECG. The AVN is the only electrical connection between the atria and the ventricles in the normal heart. The electrical impulse emerges from the AVN and is transmitted to the His-Purkinje system, specifically the common bundle of His, then the left and right bundle branches, and then to the Purkinje network, facilitating activation of ventricular muscle. The bundle of Kent is an abnormal accessory conduction pathway between the atria and ventricles present in patients that may manifest as pre-excitation in Wolff-Parkinson-White syndrome.

IV-23. The answer is E. *(Chap. 238)* The most common arrhythmia mechanism is reentry resulting from abnormal electrical impulse conduction. Reentry is defined as the circulation of an activation wave around an inexcitable obstacle. The requirements for reentry are two electrophysiologically dissimilar pathways for impulse propagation around an inexcitable region. Anatomically determined, excitable gap reentry can explain several clinically important tachycardias, such as atrioventricular reentry, atrial flutter, bundle branch reentry ventricular tachycardia, and ventricular tachycardia in scarred myocardium.

IV-24. The answer is E. *(Chap. 239)* Many cells in the heart possess the ability to spontaneously depolarize due to slow spontaneous diastolic depolarization (phase 4). The sinoatrial (SA) node, atrioventricular node, and Purkinje cells all possess this ability. However, in normal physiologic states, the SA node possesses the "steepest" phase 4 slope and thus depolarizes more rapidly than any other potential pacemaker cells (Figure IV-24). Thus, in the absence of a functioning SA node or altered conduction, other sites within the cardiac conduction system may initiate pacemaker activity, albeit typically at a slower rate than the SA node. The anatomic location of the SA node does not determine the pacemaker ability, and the SA nodal cells have no intercalated discs. Phase 0 is actually slower in nodal cells than in ventricular or atrial non-nodal cells.

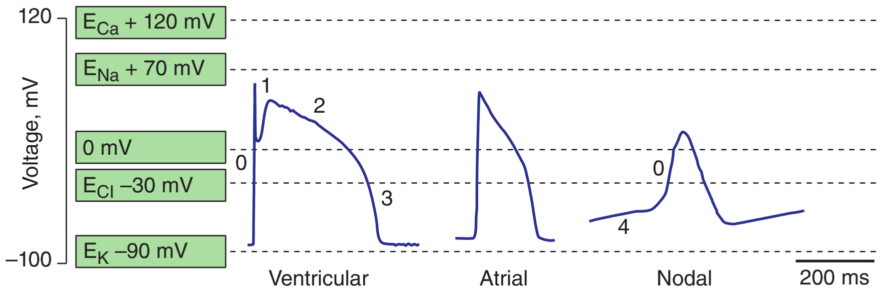


FIGURE IV-24

IV-25. The answer is C. *(Chap. 239)* Sinus bradycardia and pauses up to 3 seconds are common in young individuals, particularly in highly trained athletes. It is normal to have some heart rate variability with resting respiration. Respiratory sinus arrhythmia describes alterations in vagal tone that cause the heart rate to be slightly faster during inspiration and slower during expiration. This is not a pathologic rhythm. Given the normal conduction intervals on his baseline electrocardiogram, lack of symptoms, and normal physical examination, no further testing is warranted. It is clear that he has the ability to augment his heart rate if he has been training for this race. Wish him luck and clear him for the race.

IV-26. The answer is E. *(Chap. 239)* Sinoatrial (SA) dysfunction is often divided into intrinsic disease and extrinsic disease of the node. This is a critical distinction, as extrinsic causes are often reversible and pacemaker placement is not required. Drug toxicity is a common cause of extrinsic, reversible sinoatrial dysfunction, with common culprits including beta blockers, calcium channel blockers, lithium, narcotics, pentamidine, and clonidine. Hypothyroidism, sleep apnea, hypoxia, hypothermia, and increased intracranial pressure are all also reversible forms of extrinsic dysfunction. Radiation therapy can result in permanent dysfunction of the node and therefore is an irreversible, or intrinsic, cause of SA node dysfunction. In symptomatic patients, pacemaker insertion may be indicated.

IV-27. The answer is A. *(Chap. 239)* Failure to increase the heart rate (HR) with exercise is referred to as chronotropic incompetence. This is alternatively defined as failure to reach 85% of predicted maximal HR at peak exercise or failure to achieve an HR >100 beats/min with exercise or a maximal HR with exercise less than two standard deviations below that of an age-matched control population. Exercise testing may be useful in discriminating chronotropic incompetence from resting bradycardia and may aid in the identification of the mechanism of exercise intolerance. During exercise, this patient did not elevate his HR above 100 beats/min and did not achieve 85% of predicted maximal HR. While not definitive, the normal echocardiogram and especially normal atrial size makes heart failure with preserved ejection fraction very unlikely. Lung disease in a non-smoker with a normal chest x-ray is unlikely.

IV-28. The answer is D. *(Chap. 239)* The patient's fatigue is likely due to sinus bradycardia due to sinoatrial (SA) node dysfunction. Pharmacologic considerations are important in the evaluation and management of patients with SA nodal disease. A number of drugs modulate SA node function and are extrinsic causes of dysfunction. Beta blockers and calcium channel blockers increase sinus node recovery time. Therefore, particularly in patients with subacute SA node dysfunction, anti-arrhythmic drugs with class I and III action may promote SA node exit block and create symptomatic bradycardia. In general, such agents should be discontinued before decisions regarding the need for permanent pacing in patients with SA node disease are made.

IV-29. The answer is A. *(Chap. 240)* Atrionodal transitional connections may exhibit decremental conduction, defined as slowing of conduction with increasingly rapid rates of stimulation. This property of the atrioventricular (AV) node is physiologically important. If a very rapid atrial arrhythmia occurs, the AV node acts as a sort of "gatekeeper" to the ventricles due to its decremental conduction. Thus, in the case of atrial fibrillation (where atrial rates often exceed 300 beats/min) the ventricular rate never approaches these very rapid rates. Some accessory conduction pathways, in contrast, do not exhibit decremental conduction properties and will very rapidly conduct tachycardias (such as atrial fibrillation) to the ventricles, leading to hemodynamic collapse.

IV-30. The answer is D. *(Chap. 240)* The anatomically compact atrioventricular (AV) node (~1 × 3 × 5 mm) is situated at the apex of the triangle of Koch, which is defined by the coronary sinus ostium posteriorly, the septal tricuspid valve annulus anteriorly, and the tendon of Todaro superiorly. The compact AV node continues as the penetrating AV bundle where it immediately traverses the central fibrous body and is in close proximity to the aortic, mitral, and tricuspid valve annuli; thus, it is subject to injury in the setting of valvular heart disease or its surgical treatment. It is very common for patients to experience transient AV block after valve surgery (particularly aortic valve surgery) due to the surrounding edema. Many patients will regain normal conduction as the perioperative injury and edema decreases; however, some patients do not and require permanent pacemaker placement. It is very unlikely that this patient has developed new systemic disease such as Lyme disease, sarcoidosis, or endocarditis. Sinoatrial nodal disease would manifest as sinus bradycardia, which this patient does not have.

IV-31. **The answer is C.** *(Chap. 240)* Congenital atrioventricular block in the setting of a structurally normal heart has been seen in children born to mothers with systemic lupus erythematosus (SLE). SLE can cause sterile endocarditis in adults, but it is not common in children of mothers with SLE. Similarly, early-onset coronary artery disease, pulmonary hypertension, and occasionally cardiomyopathy is described in SLE patients but not in their children just after birth.

IV-32. **The answer is B.** *(Chap. 240)* Several infectious diseases have a predilection for the conducting system. Lyme disease may involve the heart in up to 50% of cases; 10% of patients with Lyme carditis develop atrioventricular (AV) conduction block, which is generally reversible but may require temporary pacing support. Chagas disease, which is common in Latin America, and syphilis, which is common everywhere, may produce more persistent AV conduction disturbances. Some autoimmune and infiltrative diseases may produce AV conduction block, including systemic lupus erythematosus, rheumatoid arthritis, mixed connective tissue disease, scleroderma, amyloidosis (primary and secondary), sarcoidosis, and hemochromatosis; rare malignancies also may impair AV conduction. Hyperthyroidism is not classically associated with cardiac conduction disease other than sinus tachycardia.

IV-33. **The answer is B.** *(Chap. 240)* This is Mobitz type I second-degree heart block, or Wenckebach heart block. The periodic failure of conduction in Mobitz type I block is characterized by a progressively lengthening PR interval, shortening of the RR interval, and a pause that is less than two times the immediately preceding RR interval on the electrocardiogram (ECG). The ECG complex after the pause exhibits a shorter PR interval than that immediately preceding the pause. This ECG pattern most often arises because of decremental conduction of electrical impulses in the atrioventricular node. This rhythm is usually benign and may be seen in very fit athletes due to high vagal tone.

IV-34. and 35. **The answers are B and D, respectively.** *(Chap. 241)* The patient has persistent, non–life-threatening palpitations that distress her enough to seek medical attention. A continuous Holter monitor for 24 hours is appropriate for patients in whom the symptoms happen several times over 24 hours, whereas an event monitor is triggered by the patient when symptoms occur and thus can be worn for a longer period of time, which is appropriate in this patient. There is no indication of gastrointestinal triggers, so abdominal CT would not be helpful. The atrial premature contractions are uncomplicated, do not require additional diagnostic evaluation at this time, and pose no additional health risk. Electrophysiology referral is indicated for patients with life-threatening or severe symptoms such as syncope.

IV-36. **The answer is D.** *(Chap. 241)* Wolff-Parkinson-White (WPW) pattern is almost always due to accessory pathway conduction during which electrical signals are able to propagate from atria to ventricles without first going through the atrioventricular (AV) node. As opposed to the AV node, many accessory pathways fail to exhibit decremental conduction (a slowing of conduction at increasing rates of excitation) and thus are able to very rapidly conduct fast atrial rhythms to the ventricles. At exceedingly fast rates (as might be present in atrial fibrillation) this can lead to cardiovascular collapse. The observation that Ms. Milsap's delta wave disappears and QRS complex normalizes at a relatively high heart rate is reassuring. In that case, the accessory pathway cannot conduct antegrade at a rate >120 beats/min and is very unlikely to cause serious tachyarrhythmia. The ability to augment a rapid sinus rhythm is normal for her age and does not carry any particular prognosis. The location of the accessory pathway in a septal position makes it somewhat more difficult to ablate with catheters, and the operator must take care to avoid the native AV node and the His-Purkinje system. The ability of the accessory pathway to conduct both antegrade and retrograde makes it a substrate for atrioventricular reentrant tachycardia.

IV-37. **The answer is D.** *(Chap. 241)* This patient has new atrial fibrillation. When one assesses a patient with new atrial fibrillation, it is prudent to proceed through a series of decisions systematically. If the patient is hemodynamically unstable (low blood pressure, pulmonary edema, poor mentation, low urine output) then urgent direct current cardioversion is warranted. This patient is clearly stable. The next decision hinges around rate versus rhythm control. Several studies have shown clinical equipoise between rate and rhythm control strategies, with patients randomized to the rhythm control strategies undergoing far more procedures and taking more medications than patients randomized to the rate control strategies. This is also true in patients with heart failure. Given the lack of symptoms and already controlled resting heart rate, rhythm control with either medications (amiodarone) or cardioversion is not a class I indication. In fact, a type I anti-arrhythmic such as flecainide would be contraindicated as it was shown to increase mortality in patients with coronary disease. The final question revolves around anticoagulation. Patients with atrial fibrillation have varying degrees of risk of thromboembolic events. Patients are stratified into risk categories by assessing set risk factors. One can remember the CHADS$_2$ mnemonic to recall each point of the risk scoring system (congestive heart failure, hypertension, age >75, diabetes, and stroke/cerebrovascular accident [which receives 2 points]). A more sensitive score includes vascular disease, age >65, and female sex (CHA$_2$DS$_2$-VASc). Any combined score >1 warrants systemic anticoagulation. Patients with a 0 score do not require systemic anticoagulation and can take full-strength aspirin. A score of 1 is intermediate and requires an in-depth discussion with the patient about his or her risk threshold for anticoagulation. Many experts recommend systemic anticoagulation with CHADS$_2$ score = 1. This patient has a CHADS$_2$ score = 3 (congestive heart failure, hypertension, age) and therefore warrants systemic anticoagulation.

IV-38. **The answer is E.** *(Chap. 241)* This rhythm is multifocal atrial tachycardia (MAT), which is easily confused with atrial fibrillation due to its irregularly irregular nature. However, MAT is distinguished by the multiple different P waves present (at least three different P wave morphologies). MAT is classically present in patients with severe pulmonary disease, and is exacerbated in the presence of acute illness. No anticoagulation is needed for MAT, and direct current cardioversion is not efficacious. Some patients respond to the non-dihydropyridine calcium channel blockers (diltiazem and verapamil), and amiodarone has some limited effect. In this patient controlling the underlying cause of her tachycardia (pain and dehydration) is the most appropriate first therapy.

IV-39. **The answer is D.** *(Chap. 241)* Termination with atrioventricular (AV) node blocking agents or maneuvers, such as the Valsalva maneuver, are consistent with mechanisms dependent on AV nodal conduction, such as orthodromic AV reentry tachycardia (ORT) or AV node reentry tachycardia (AVNRT). Atrial flutter and atrial tachycardia unlikely typically will not respond to these maneuvers. The 12-lead electrocardiogram shows a narrow complex tachycardia with a regular atrial rate and 1:1 AV response. Using the algorithms shown in Figure IV-39B the most likely mechanisms are AVNRT or ORT. The P wave can be seen in the ST segment (arrows) and appears to be positive in lead III and negative in leads I and aVL, which suggests a left free wall origin. Ablation of the left free wall accessory pathway eliminated further episodes of SVT.

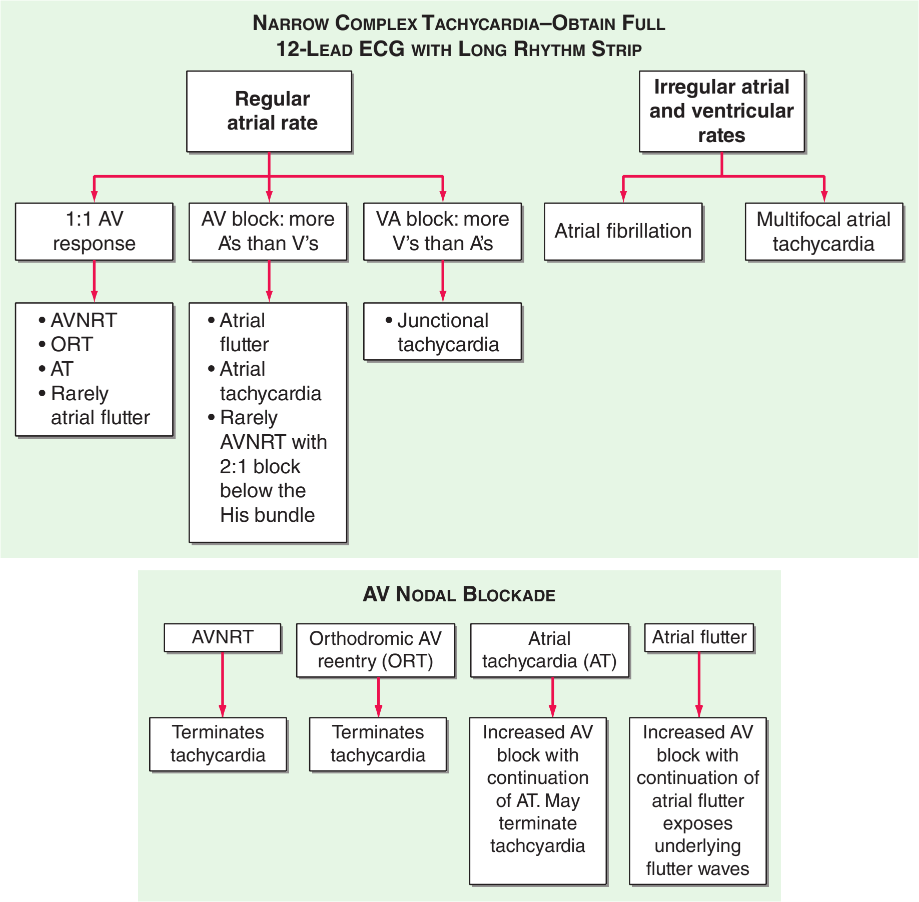

Narrow Complex Tachycardia–Obtain Full 12-Lead ECG with Long Rhythm Strip
Regular atrial rate
Irregular atrial and ventricular rates
1:1 AV response
AV block: more A's than V's
VA block: more V's than A's
Atrial fibrillation
Multifocal atrial tachycardia
• AVNRT
• ORT
• AT
• Rarely atrial flutter
• Atrial flutter
• Atrial tachycardia
• Rarely AVNRT with 2:1 block below the His bundle
• Junctional tachycardia
AV Nodal Blockade
AVNRT
Orthodromic AV reentry (ORT)
Atrial tachycardia (AT)
Atrial flutter
Terminates tachycardia
Terminates tachycardia
Increased AV block with continuation of AT. May terminate tachcyardia
Increased AV block with continuation of atrial flutter exposes underlying flutter waves

FIGURE IV-39B *Abbreviation:* VA, ventricular-atrial.

IV-40. **The answer is C.** *(Chaps. 242 and 273)* This patient has sinus tachycardia. The 1:1 relationship between P wave and QRS with normal P wave axis, PR duration, and QRS duration all signify sinus tachycardia. Sinus tachycardia is usually due to an underlying cause (Table IV-40). In this case, you should strongly suspect pulmonary embolism given the patient's neoplastic disease, distended jugular vein, and hypoxia in the setting of clear lungs on examination. Given the high likelihood of pulmonary embolism, systemic anticoagulation should be initiated immediately. A contrast CT scan of the chest would be indicated diagnostically.

TABLE IV-40 Common Causes of Physiologic Sinus Tachycardia

1. Exercise
2. Acute illness with fever, infection, pain
3. Hypovolemia, anemia
4. Hyperthyroidism
5. Pulmonary insufficiency
6. Drugs that have sympathomimetic, vagolytic, or vasodilator properties, e.g., albuterol, theophylline, tricyclic antidepressants, nifedipine, hydralazine
7. Pheochromocytoma

IV-41. **The answer is E.** *(Chap. 242)* This patient has postural orthostatic tachycardia syndrome (POTS). POTS is characterized by symptomatic sinus tachycardia that occurs with postural change from a supine position to standing. The sinus rate increases by 30 beats/min or to >120 beats/min within 10 minutes of standing and in the absence of hypotension. Symptoms are often similar to those in patients with inappropriate sinus tachycardia. POTS is sometimes due to autonomic dysfunction following a viral illness and may resolve spontaneously over 3–12 months. Volume expansion with salt supplementation, oral fludrocortisone, compression stockings, and the α-agonist midodrine, often in combination, can be helpful. Exercise training has also been purported to improve symptoms.

IV-42. **The answer is D.** *(Chap. 243)* This patient has focal atrial tachycardia. The arrows (which are a nice clue in the question!) indicate the ectopic atrial activity. While one could consider that this might be sinus tachycardia, the rate far exceeds the patient's maximal predicted heart rate (220 – age) and obviates the possibility of any sinus rhythm. Any maneuver or pharmacologic therapy aimed at producing transient atrioventricular (AV) nodal block (e.g., Valsalva, carotid massage, adenosine) may briefly slow the ventricular response. However, since focal atrial tachycardia does not rely on the AV node for continuation it is rare that transient AV nodal block will terminate the arrhythmia. Beta blockers or non-dihydropyridine calcium channel blockers can lead to sustained improvement in heart rate. Pacemakers have no role here.

IV-43. **The answer is A.** *(Chap. 243)* Focal atrial tachycardia (AT) accounts for ~10% of paroxysmal supraventricular tachycardias in patients referred for catheter ablation. Nonsustained AT is commonly observed on 24-hour ambulatory electrocardiogram recordings, and the prevalence increases with age. In fact, frequent atrial ectopy and nonsustained AT is often a precursor to more significant arrhythmias such as atrial fibrillation and flutter. Though unsustained, frequent atrial ectopy or short bursts of AT may be symptomatic and require therapy similar to that required for focal AT. AT can occur in the absence of structural heart disease or may be associated with any condition that causes atrial fibrosis, including prior catheter ablation. Areas of fibrosis can be a nidus for abnormal automaticity from damaged cells or micro reentry within zones of slow conduction within and on the border of fibrotic areas. Sympathetic stimulation is a promoting factor, and the emergence of AT can be a sign of underlying illness.

IV-44. **The answer is A.** *(Chap. 243)* This is a focal atrial tachycardia (AT). Focal AT can be due to abnormal automaticity, triggered automaticity, or a small reentry circuit confined to the atrium or atrial tissue extending into a pulmonary vein, the coronary sinus, or vena cava. Because it is not dependent on atrioventricular (AV) nodal conduction, AT will not terminate with AV block, and the atrial rate will not be affected, which distinguishes AT from most AV nodal–dependent supraventricular tachycardias (SVTs), such as AV nodal reentry and AV reentry using an accessory pathway (Figure IV-44). An accelerated

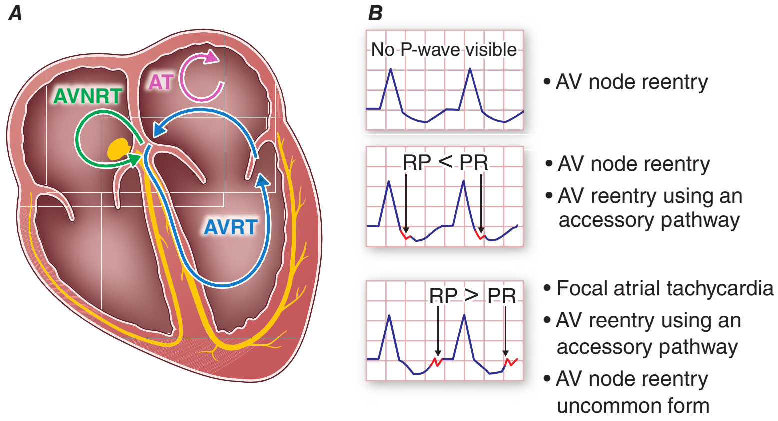

A
AVNRT
AT
AVRT
B
No P-wave visible
• AV node reentry
RP < PR
• AV node reentry
• AV reentry using an accessory pathway
RP > PR
• Focal atrial tachycardia
• AV reentry using an accessory pathway
• AV node reentry uncommon form

FIGURE IV-44 Common mechanisms underlying paroxysmal supraventricular tachycardia along with typical R-P relationships. ***(A)*** Schematic showing a four-chamber view of the heart with atrioventricular node and specialized conduction tissue (His-Purkinje) in yellow. Atrial tachycardia (AT; red circuit) is confined completely to atrial tissue. Atrioventricular nodal reentry tachycardia (AVNRT; green circuit) uses atrioventricular (AV) nodal and perinodal atrial tissue. Atrioventricular reentry tachycardia (AVRT; blue circuit) uses atrial and ventricular tissue, accessory pathway between the ventricle and atrium, AV node, and the His-Purkinje tissue as part of the reentry circuit. ***(B)*** Typical relation of the P wave to QRS, commonly described as the R-P to P-R relationships for the different tachycardia mechanisms.

warm-up phase after initiation or cool-down phase prior to termination also favors AT rather than AV nodal–dependent SVT, as this is a common observation with triggered automaticity. P waves are often discrete, with an intervening isoelectric segment, in contrast to atrial flutter and macro reentrant AT (Figure IV-44) because atrial activation from a focal source occurs though a small portion of the tachycardia cycle. Since conduction occurs normally through the AV node–His-Purkinje system, the QRS in AT is usually narrow.

IV-45. **The answer is C.** *(Chap. 244)* Atrioventricular nodal reentry tachycardia (AVNRT) is the most common form of paroxysmal supraventricular tachycardia, representing ~60% of cases referred for catheter ablation. It most commonly manifests in the second to fourth decades of life, often in women. It is often well tolerated, but rapid tachycardia, particularly in the elderly, may cause angina, pulmonary edema, hypotension, or syncope. It is not usually associated with structural heart disease. The mechanism is reentry involving the AV node and the perinodal atrium, made possible by the existence of multiple pathways for conduction from the atrium into the AV node that are capable of conduction in two directions. Most forms of AVNRT utilize a slowly conducting AV nodal pathway that is located as a right inferior extension that extends from the compact AV node near the His bundle, inferiorly along the tricuspid valve annulus to the floor of the coronary sinus. In typical forms, the conduction time from the compact AV node region to the atrium is similar to that from the compact node to the His bundle and ventricles, such that atrial activation occurs at about the same time as ventricular activation. The P wave is therefore inscribed during, slightly before, or slightly after the QRS and can be difficult to discern. Often the P wave is seen at the end of the QRS complex as a pseudo-R’ in lead V_1 and pseudo-S waves in leads II, III, and aVF.

IV-46. **The answer is B.** *(Chap. 244)* Junctional ectopic tachycardia (JET) is due to automaticity within the atrial ventricular (AV) node. It is rare in adults and more frequently encountered as an incessant tachycardia in children, often in the perioperative period of surgery for congenital heart disease. It presents as a narrow QRS tachycardia, often with ventriculoatrial block, such that AV dissociation is present. JET can occur as a manifestation of increased adrenergic tone and may be seen after administration of isoproterenol, particularly after catheter ablation in the perinodal region. It may also occur for a short period of time after ablation for AV nodal reentry tachycardia.

IV-47. **The answer is E.** *(Chap. 244)* The disease associations with accessory pathways (APs) are useful to remember, as some may present in childhood (e.g., Ebstein anomaly) but others may also present in adulthood. APs occur in 1 in 1500 to 2000 people and are associated with a variety of arrhythmias including narrow-complex paroxysmal supraventricular tachycardia, wide-complex tachycardias, and, rarely, sudden death. Most patients have structurally normal hearts, but APs are associated with Ebstein anomaly of the tricuspid valve and forms of hypertrophic cardiomyopathy including PRKAG2 mutations, Danon disease, and Fabry disease.

IV-48. **The answer is B.** *(Chap. 244)* This electrocardiogram (ECG) is pre-excited atrial fibrillation (AF) due to conduction over a left free wall accessory pathway (AP). The ECG shows rapid irregular QRS complexes that represent fusion between conduction over the atrioventricular node and left free wall AP. AF and atrial flutter are potentially life-threatening if the AP allows very rapid repetitive conduction. Approximately 25% of APs causing pre-excitation allow minimum R-to-R intervals of <250 ms during AF and are associated with a higher risk of inducing ventricular fibrillation and sudden death. Pre-excited AF presents as a wide-complex, very irregular rhythm. During AF, the ventricular rate is determined by the conduction properties of the AP and the AV node. The QRS complex can appear quite bizarre and change on a beat-to-beat basis due to the variability in the degree of fusion from activation over the AV node and AP, or all beats may be due to conduction over the AP.

IV-49. **The answer is E.** *(Chap. 244)* Ventricular activation from the Purkinje system may depolarize the ventricular end of the accessory pathway (AP) and prevent atrial wavefront conduction over the AP. Slowing AV nodal conduction without slowing AP conduction can thereby facilitate AP conduction and dangerously accelerate the ventricular rate. Administration of atrioventricular nodal–blocking agents including oral or IV verapamil, diltiazem, beta blockers, IV adenosine, and IV amiodarone are contraindicated during pre-excited atrial fibrillation. Rapid pre-excited tachycardia should be treated with electrical cardioversion or IV procainamide or ibutilide, which may terminate the arrhythmia or slow the ventricular rate.

IV-50. The answer is B. *(Chap. 245)* Common or typical right atrial flutter is due to a circuit that revolves around the tricuspid valve annulus, bounded anteriorly by the annulus and posteriorly by functional conduction block in the crista terminalis. The wavefront passes between the inferior vena cava and the tricuspid valve annulus, known as the sub-Eustachian or cavotricuspid isthmus, where it is susceptible to interruption by catheter ablation. Thus, common atrial flutter is also known as cavotricuspid isthmus-dependent atrial flutter. This circuit most commonly revolves in a counterclockwise direction (as viewed looking toward the tricuspid annulus from the ventricular apex), which produces the characteristic negative sawtooth flutter waves in leads II, III, and aVF and positive P waves in lead V_1. When the direction is reversed, clockwise rotation produces the opposite P wave vector in those leads. The atrial rate is typically 240–300 beats/min but may be slower in the presence of atrial disease or anti-arrhythmic drugs. It often conducts to the ventricles with 2:1 AV block, creating a regular tachycardia at 150 beats/min, with P waves that may be difficult to discern. Vagal maneuvers that increase AV nodal block

TABLE IV-50 CHA_2DS_2-VASc Risk Assessment and Oral Anticoagulants

Risk Factors	Points	CHA_2DS_2-VASc Score	Estimated Annual Stroke Rate[a]
C—congestive heart failure	1	0	0
H—hypertension	1	1	1.3%
A—age ≥75 y	2	2	2.2%
D—diabetes mellitus	1	3	3.2%
S—stroke or TIA, embolus	2	4	4.0%
V—vascular disease	1	5	6.7%
A—age 65–75 y	1	6–9	>9%
Sex—female	1		

Anticoagulants	Mechanism	Excretion	Dosing Considerations	Risk/Benefit
Warfarin	Vitamin K antagonist	Liver	Adjusted to INR 2–3 days to therapeutic effect Multiple drug/food interactions (e.g., amiodarone)	Major hemorrhage: 1% per year Intracranial hemorrhage: 0.1–0.6% per year Risk of bleeding increases with INR >3.5 Inexpensive
Dabigatran[b]	Thrombin inhibitor	Kidney		
		CCr >30 mL/min	150 mg bid	Onset of action within hours
		CCr 15–30 mL/min	75 mg bid P-glycoprotein substrate (inducers—rifampin, reduce concentration) (inhibitors—amiodarone, verapamil, dronedarone, quinidine) Proton pump inhibitors may reduce absorption	No reversal agent for bleeding
Rivaroxaban	Xa inhibitor	Kidney	P-glycoprotein substrate	No reversal agent for bleeding
		CCr ≥50 mL/min	20 mg daily	
		CCr 15–50 mL/min	15 mg daily	
Apixaban	Xa inhibitor	Kidney and liver	P-glycoprotein substrate	No reversal agent for bleeding
		Any two of: Cr >1.5 mg/dL, age >80 years, or wt <60 kg	5 mg bid 2.5 mg bid	

[a] Data from Lip GY et al: Atrial fibrillation. *Lancet* 379:648, 2012.

[b] U.S. Food and Drug Administration recommended dosing; other regimens are available outside the United States.

Abbreviations: CCr, creatinine clearance; Cr, creatinine; INR, international normalized ratio; TIA, transient ischemic attack; wt, weight.

will typically expose flutter waves, allowing diagnosis. The risk of thromboembolic events is felt to be similar to that associated with atrial fibrillation. Anticoagulation is warranted prior to conversion for episodes more than 48 hours in duration and chronically for patients at increased risk of thromboembolic stroke based on the CHA_2DS_2-VASc scoring system (Table IV-50).

IV-51. The answer is A. *(Chap. 245)* Initial management of atrial flutter is similar to that for atrial fibrillation. Electrical cardioversion is warranted for hemodynamic instability or severe symptoms. Otherwise, rate control can be achieved with administration of AV nodal–blocking agents, but this is often more difficult than for atrial fibrillation. The risk of thromboembolic events is felt to be similar to that associated with atrial fibrillation. Anticoagulation is warranted prior to conversion for episodes more than 48 hours in duration and chronically for patients at increased risk of thromboembolic stroke based on the CHA_2DS_2-VASc scoring system. For a first episode of atrial flutter, conversion to sinus rhythm with no anti-arrhythmic drug therapy is reasonable. For recurrent episodes, anti-arrhythmic drug therapy with sotalol, dofetilide, disopyramide, and amiodarone may be considered, but >70% of patients experience recurrences. For recurrent episodes of common atrial flutter, catheter ablation of the cavotricuspid isthmus abolishes the arrhythmia in >90% of patients with a low risk of complications that are largely related to vascular access, and rarely heart block.

IV-52. The answer is B. *(Chap. 246)* Atrial fibrillation (AF) is the most common sustained arrhythmia and is a major public health problem. Prevalence increases with age, and >95% of AF patients are >60 years of age. The prevalence by age 80 is ~10%. The lifetime risk of developing AF for a 40-year-old male is ~25%. AF is slightly more common in men than women and more common in whites than blacks. Risk factors for developing AF in addition to age and underlying cardiac disease include hypertension, diabetes mellitus, cardiac disease, obesity, and sleep apnea. AF is associated with a 1.5- to 1.9-fold increased risk of mortality after controlling for underlying heart disease. AF is also associated with a risk of developing heart failure and vice-versa—patients with heart failure have an increased risk of developing AF. AF increases the risk of stroke by fivefold and is estimated to be the cause of 25% of strokes.

IV-53. The answer is D. *(Chap. 246)* Clinical consequences of atrial fibrillation (AF) are related to rapid ventricular rates, loss of atrial contribution to ventricular filling, and predisposition to thrombus formation in the left atrial appendage with potential embolization. Patients with AF are at a markedly increased risk of stroke and other embolic events. Rapid ventricular rate may impede ventricular filling and lead to low cardiac output. Effective left atrial contraction typically contributes 10–35% to stroke volume. Loss of this in AF may impact cardiac output in patients with poor left ventricular or right ventricular function.

IV-54. The answer is A. *(Chap. 246)* New-onset atrial fibrillation (AF) that produces severe hypotension, pulmonary edema, or angina should immediately be electrically cardioverted starting with a QRS synchronous shock of 200 J, ideally after sedation or anesthesia is achieved. Greater shock energy and different electrode placements may be tried if the shock fails to terminate AF. Transcutaneous pacing has no role in the treatment of tachycardias. All other listed treatments can be useful in the diagnosis or treatment of *hemodynamically stable* supraventricular tachycardia.

IV-55. The answer is E. *(Chap. 246)* Even though this patient has a lower CHA_2DS_2-VASc score, she has rheumatic mitral stenosis and therefore is at high risk for stroke with atrial fibrillation (AF). The major options for anticoagulation in AF are the antithrombin inhibitor dabigatran, factor Xa inhibitors rivaroxaban, apixaban, and edoxaban; and the vitamin K antagonist warfarin. Antiplatelet agents alone are generally not sufficient. In nonvalvular AF, warfarin reduces the annual risk of stroke by 64% compared with placebo and by 37% compared with antiplatelet therapy. Patients with AF with an increased risk of stroke also have an increased risk of venous thromboembolism, which appears to be lower with oral anticoagulation. The direct-acting anticoagulants, dabigatran, rivaroxaban, apixaban, and edoxaban were noninferior to warfarin in individual trials, and analysis of pooled data suggests superiority to warfarin by small absolute margins of 0.4–0.7% in reduction of mortality, stroke, major bleeding, and intracranial hemorrhage. Warfarin is the agent required for patients with rheumatic mitral stenosis or mechanical heart valves. The newer, direct-acting anticoagulants have not been tested in rheumatic heart disease, and a direct thrombin inhibitor did not prevent thromboemboli in patients with mechanical heart valves.

IV-56. **The answer is B.** *(Chap. 247)* The rhythm strip in Figure IV-56 demonstrates multifocal premature ventricular contractions (PVCs). The two PVCs shown have different morphologies. Atrial flutter would have the stereotypical sawtooth P waves which are not present. Ventricular tachycardia (VT) would have repeated wide complex tachycardia—nonsustained VT is defined as VT that lasts <30 seconds, whereas VT lasting >30 seconds or requiring intervention for termination is deemed sustained VT.

IV-57. **The answer is D.** *(Chap. 247)* Diltiazem is a *non*-dihydropyridine calcium channel blocker. Flecainide is a sodium channel blocker. Metoprolol is a β-adrenergic receptor blocker. Verapamil is also a non-dihydropyridine calcium channel blocker. Sotalol (and dofetilide) block the delayed rectifier potassium channel IKr, prolonging action potential duration (QT interval) and the cardiac refractory period, known as the class III anti-arrhythmic drug effect. Sotalol also has beta-blocking activity.

IV-58. **The answer is E.** *(Chap. 248)* Premature ventricular contractions (PVCs) can be due to automaticity or reentry. They are often sensitive to sympathetic stimulation and can be a sign of increased sympathetic tone; myocardial ischemia; hypoxia; electrolyte abnormalities, particularly hypokalemia; or underlying heart disease. During myocardial ischemia or in association with other heart disease, PVCs can be a harbinger of sustained ventricular tachycardia or ventricular fibrillation. The electrocardiogram characteristics of the arrhythmia are often suggestive of whether structural heart disease is present. PVCs with smooth uninterrupted contours and sharp QRS deflections suggest an ectopic focus in relatively normal myocardium, whereas broad notching and slurred QRS deflections suggest a diseased myocardial substrate. The QRS morphology also suggests the likely site of origin within the ventricle. PVCs that have a dominant S wave in V_1, referred to as left bundle branch block–like configuration, originate from the right ventricle or interventricular septum. Those with a dominant R wave in V_1 originate from the left ventricle. A superior frontal plane axis (negative in II, III, and aVF) indicates initial depolarization of the inferior wall (diaphragmatic aspect of the heart), whereas an inferior frontal plane axis (positive in II, III, and aVF) indicates an origin in the cranial aspect of the heart. The location of arrhythmia origin often suggests the nature of underlying heart disease. Most ventricular arrhythmias that are not associated with structural heart disease have a left bundle branch block–like configuration. PVCs with right bundle branch configuration are more likely to be associated with structural heart disease. Multiple morphologies of PVCs (multifocal PVCs) are also more likely to indicate structural heart disease.

IV-59. **The answer is B.** *(Chap. 248)* A family history of sudden death should prompt evaluation for genetic syndromes associated with sudden death, including cardiomyopathy, long QT syndrome, and arrhythmogenic right ventricular cardiomyopathy (ARVC). Any abnormality on the 12-lead electrocardiogram (ECG) warrants further evaluation. Repolarization abnormalities are seen in a number of genetically determined syndromes associated with sudden death, including the long QT syndrome, Brugada syndrome, ARVC, and hypertrophic cardiomyopathy. This ECG shows ST elevation in V_1 and V_2 typical of the Brugada syndrome.

IV-60. **The answer is A.** *(Chap. 248)* During and soon after acute myocardial infarction (MI), premature ventricular contractions (PVCs) and nonsustained ventricular tachycardia (VT) are common and can be an early manifestation of ischemia and a harbinger of subsequent ventricular fibrillation (VF). Treatment with β-adrenergic blockers and correction of hypokalemia and hypomagnesemia reduce the risk of VF. Routine administration of anti-arrhythmic drugs such as lidocaine does not reduce mortality and is not indicated for suppression of PVCs or asymptomatic nonsustained VT, but it may be implemented transiently if an episode of sustained VT or VF occurs, with the goal of reducing the likelihood of a subsequent episode.

IV-61. The answer is E. *(Chap. 248)* The use of anti-arrhythmic drugs whose major action is blockade of the cardiac sodium channel (flecainide, propafenone, mexiletine, quinidine, and disopyramide) is avoided in patients with structural heart disease because of a risk of pro-arrhythmia, negative inotropic effects, and increased mortality. Therapy with the potassium channel blocker dofetilide does not reduce mortality. Amiodarone suppresses ventricular ectopy and reduces sudden death, but it does not improve overall survival. Implantable cardioverter defibrillators are the major therapy to protect against sudden death in patients at high risk and are recommended for those with left ventricular ejection fraction <0.35 and New York Heart Association class II and III heart failure, in whom they reduce mortality from 36 to 29%, over 5 years.

IV-62. The answer is B. *(Chap. 249)* Differentiating supraventricular tachycardia (SVT) from ventricular tachycardia (VT) can often be difficult. In the presence of known heart disease VT is the most likely diagnosis of a wide QRS tachycardia. Hemodynamic stability during the arrhythmia does not exclude VT. A number of electrocardiogram criteria have been evaluated to distinguish SVT with aberrancy from VT. The presence of atrioventricular dissociation is usually a reliable marker for VT (Figure IV-62), but P waves can be difficult to define. A P wave following each QRS does not exclude VT because 1:1 conduction from ventricle to atrium can occur. A monophasic R wave or RS complex in aVR or concordance from V_1 to V_6 of monophasic R or S waves are also relatively specific for VT.

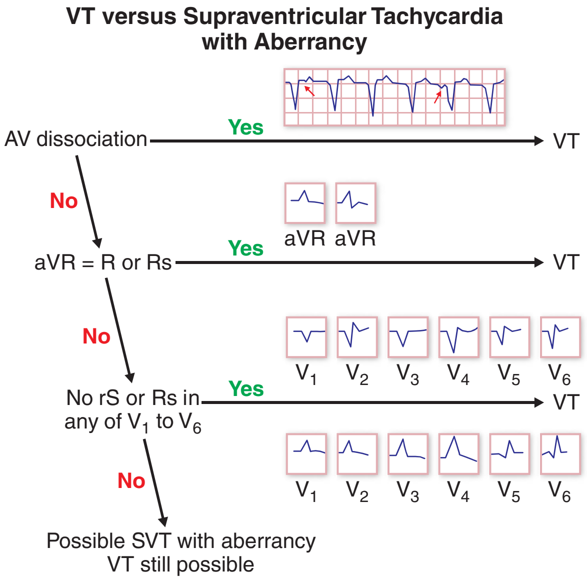

VT versus Supraventricular Tachycardia with Aberrancy
AV dissociation
Yes
VT
No
aVR aVR
aVR = R or Rs
Yes
VT
No
V1 V2 V3 V4 V5 V6
No rS or Rs in any of V1 to V6
Yes
VT
V1 V2 V3 V4 V5 V6
No
Possible SVT with aberrancy
VT still possible

FIGURE IV-62 *Abbreviations:* AV, atrioventricular; SVT, supraventricular tachycardia; VT, ventricular tachycardia.

IV-63. The answer is B. *(Chap. 249)* This patient has arrhythmogenic right ventricular cardiomyopathy (ARVC). ARVC is a rare genetic disorder most commonly due to mutations in genes encoding cardiac desmosomal proteins. Approximately 50% have a familial transmission with autosomal dominant inheritance. A less common, autosomal recessive form is associated with cardiocutaneous syndromes that include Naxos disease and Carvajal syndrome. Patients typically present between the second and fifth decade with palpitations, syncope, or cardiac arrest due to sustained monomorphic ventricular tachycardia (VT), although polymorphic VT can also occur. Fibrosis and fibro-fatty replacement most commonly involves the right ventricular myocardium, and it provides the substrate for reentrant VT that usually has a left bundle branch block–like configuration, consistent with the right ventricular origin and can resemble idiopathic VT. The sinus rhythm electrocardiogram suggests the disease in >85% of patients, most often showing T wave inversions in V_1–V_3 (Figure IV-63B). Delayed activation of the right ventricle may cause a widened QRS (>110 ms) in the right precordial leads and a prolonged S wave upstroke in those leads, and occasionally a deflection at the end of the QRS known as an "epsilon" wave (arrows).

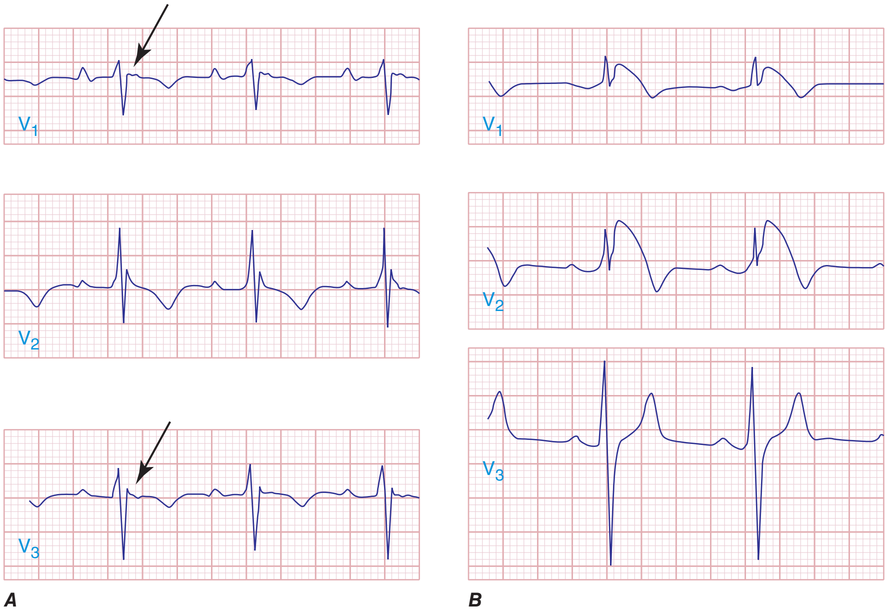


FIGURE IV-63B

IV-64. **The answer is D.** *(Chap. 249)* Idiopathic ventricular tachycardia (VT) in patients without structural heart disease usually presents with palpitations, light-headedness, and occasionally syncope, often provoked by sympathetic stimulation during exercise or emotional upset. The QRS morphology of the arrhythmia suggests the diagnosis. The sinus rhythm ECG is normal. Cardiac imaging shows normal ventricular function and no evidence of ventricular scar. Occasionally a patient with structural heart disease is found to have concomitant idiopathic VT, unrelated to the structural disease. Sudden death is rare. Outflow tract VTs originate from a focus, usually with features consistent with triggered automaticity. The arrhythmia may present with sustained VT, nonsustained VT, or premature ventricular contractions often provoked by exercise or emotional upset. Repeated bursts of nonsustained VT, which may occur incessantly, are known as repetitive monomorphic VT and can cause tachycardia-induced cardiomyopathy with depressed ventricular function that recovers after suppression of the arrhythmia. Most originate in the right ventricular outflow tract, which gives rise to VT that has a left bundle branch block configuration in V_1 and an axis that is directed inferiorly, with tall R waves in II, III, and aVF. Idiopathic VT can also arise in the left ventricular outflow tract or in sleeves of myocardium that extend along the aortic root. Left ventricular origin is suspected when leads V_1 or V_2 have prominent R waves.

IV-65. **The answer is A.** *(Chap. 250)* This rare familial syndrome is due to mutations in the cardiac ryanodine receptor and less commonly, the sarcoplasmic calcium binding protein, calsequestin-2. These mutations result in abnormal sarcoplasmic calcium handling and polymorphic ventricular arrhythmias that resemble those seen with digitalis toxicity. The ventricular tachycardia (VT) is polymorphic or has a characteristic alternating QRS morphology termed bidirectional VT. Patients usually present during childhood with exercise or emotion-induced palpitations, syncope, or cardiac arrest. β-Adrenergic blockers (e.g., nadolol and propranolol) and an implantable defibrillator are usually recommended. Verapamil or flecainide or surgical left cardiac sympathetic denervation reduces or prevents recurrent VT in some patients. Desmosomal protein mutations are involved in arrhythmogenic right ventricular cardiomyopathy. Potassium and sodium channel mutations are involved in long QT syndrome. Sarcomeric protein mutations are involved in hypertrophic cardiomyopathy.

IV-66. The answer is E. *(Chap. 250)* This patient is in ventricular fibrillation. Immediate defibrillation is required and treatment should proceed along advanced cardiac life support protocol. Defibrillation in this case should precede administration of oxygen. Medications will not be effective in the absence of circulation.

IV-67. The answer is A. *(Chap. 251)* A substantial number of patients who receive an implantable cardioverter defibrillator (ICD) can be expected to have an arrhythmia that is terminated by the ICD, either by a shock or anti-tachycardia pacing. Although this is an expected event, it can be a sign of impending instability, deterioration of cardiac function, or emergence of a new arrhythmia or ICD malfunction, and therefore requires evaluation. Interrogation of the ICD is crucial after a patient reports a shock or symptoms of arrhythmia to confirm that the therapy was indeed delivered for a ventricular arrhythmia and not for lead malfunction or an atrial arrhythmia. After a single shock or two successive shocks occurring within a few seconds, and in the absence of other symptoms to suggest arrhythmia or ischemia, patients have the option of waiting until the next working day or using remote monitoring to transmit device interrogation data to their physician. However, occurrence of multiple ICD shocks constitutes a medical emergency and warrants immediate medical attention, usually by summoning emergency medical responders.

IV-68. The answer is C. *(Chap. 252)* The New York Heart Association (NYHA) classification is a tool to define criteria that describe the functional ability and clinical manifestations of patients in heart failure. It is also used in patients with pulmonary hypertension. These criteria have been shown to have prognostic value with worsening survival as class increases. They are also useful to clinicians when reading studies to understand the entry and exclusion criteria of large clinical trials. Class I is used for patients with no limiting symptoms, class II is for patients with slight or mild limitation, class III implies no symptoms at rest but dyspnea or angina or palpitations with little exertion and patients are moderately limited, and class IV is severely limited so that even minimal activity causes symptoms. There is no NYHA Class V. Treatment guidelines also frequently base recommendations on these clinical stages. This patient has symptoms with mild exertion but is comfortable at rest; therefore he is NYHA class III.

IV-69. The answer is E. *(Chap. 252)* The patient presents with evidence of heart failure by history and physical examination confirms this diagnosis. The warm extremities make a high-output state more likely than low cardiac output. Physical examination also shows exophthalmos and a fine tremor suggestive of hyperthyroidism. Thyrotoxicosis, along with anemia, nutritional disorders, and systemic arteriovenous shunting can all cause high-output heart failure. While anemia is also a cause of high-output heart failure, in this case the eye examination and tremor make hyperthyroidism more likely than anemia. Although systolic and diastolic dysfunction are more common causes of heart failure, disorders associated with high-output state are often reversible; therefore a diagnosis should be pursued when clinical clues suggest this may be present.

IV-70. The answer is C. *(Chap. 252)* In the failing heart, multiple systems are upregulated to attempt to maintain cardiac output through augmenting sodium and water retention (angiotensin II, aldosterone, arginine vasopressin) and myocardial contractility (norepinephrine). While initially helpful in maintaining cardiac output, these adaptations become deleterious by contributing to the development of adverse myocardial remodeling and the congestive state. Also deleterious is the upregulation of inflammatory systems (including tumor necrosis factor). Counterregulatory natriuretic peptides (such as B-type natriuretic peptide) are also upregulated and aid in reducing systemic vascular resistance and natriuresis. In the state of heart failure, transcriptional and posttranscriptional changes in the myocyte lead to calcium leakage through the sarcoplasmic reticular membrane, and therefore decreased calcium uptake in the sarcoplasmic reticulum.

IV-71. The answer is C. *(Chap. 252)* B-type natriuretic peptide and its N-terminal fraction are increased in heart failure states, and on the population level contribute to prognosis in heart failure states. However, it is important to recognize that natriuretic peptide levels increase with age and renal impairment, are more elevated in women, and can be elevated in right heart failure from any cause. Levels can be falsely low in obese patients. Other biomarkers, such as soluble ST-2 and galectin-3, are newer biomarkers that can be used for determining the prognosis of heart failure patients.

IV-72. The answer is C. *(Chap. 252)* Left ventricular remodeling develops in response to a series of complex events that occur at the cellular and molecular levels. These changes include (1) myocyte hypertrophy; (2) alterations in the contractile properties of the myocyte; (3) progressive loss of myocytes through necrosis, apoptosis, and autophagic cell death; (4) β-adrenergic desensitization; (5) abnormal myocardial energetics and metabolism; and (6) reorganization of the extracellular matrix with dissolution of the organized structural collagen weave surrounding myocytes and subsequent replacement by an interstitial collagen matrix that does not provide structural support to the myocytes. The biologic stimuli for these profound changes include mechanical stretch of the myocyte, circulating neurohormones (e.g., norepinephrine, angiotensin II), inflammatory cytokines (e.g., tumor necrosis factor), other peptides and growth factors (e.g., endothelin), and reactive oxygen species (e.g., superoxide). The sustained overexpression of these biologically active molecules contributes to the progression of heart failure by virtue of the deleterious effects they exert on the heart and the circulation.

IV-73. The answer is A. *(Chap. 252)* Orthopnea, which is defined as dyspnea occurring in the recumbent position, is usually a later manifestation of heart failure (HF) than is exertional dyspnea. It results from redistribution of fluid from the splanchnic circulation and lower extremities into the central circulation during recumbency, with a resultant increase in pulmonary capillary pressure. Nocturnal cough is a common manifestation of this process and a frequently overlooked symptom of HF. Orthopnea generally is relieved by sitting upright or sleeping with additional pillows. Although orthopnea is a relatively specific symptom of HF, it may occur in patients with abdominal obesity or ascites and patients with pulmonary disease whose lung mechanics favor an upright posture.

IV-74. The answer is E. *(Chap. 252)* Although dyspnea on exertion, orthopnea, and paroxysms of nocturnal dyspnea are common heart failure symptoms, patients with heart failure (HF) also may present with gastrointestinal, urologic, or neurologic symptoms. Anorexia, nausea, and early satiety associated with abdominal pain and fullness are common complaints and may be related to edema of the bowel wall and/or a congested liver. Congestion of the liver and stretching of its capsule may lead to right upper quadrant pain. Cerebral symptoms such as confusion, disorientation, and sleep and mood disturbances may be observed in patients with severe HF, particularly elderly patients with cerebral arteriosclerosis and reduced cerebral perfusion. Nocturia is common in HF and may contribute to insomnia.

IV-75. The answer is E. *(Chap. 253)* Although therapeutic targets in heart failure with reduced ejection fraction are relatively abundant and guided by the targets of disease modification, trials in heart failure with preserved ejection fraction (HFpEF) have been largely disappointing. Angiotensin-converting enzyme inhibitors (option A) have been studied in many mechanistic studies and shown no convincing mortality benefit in HFpEF. Similarly, angiotensin receptor blockers (option B) were studied in the CHARM-Preserved and I-PRESERVE studies and found no mortality benefit. Sildenafil (a PDE-5 inhibitor) was shown to improve filling pressures and right ventricular function in patients with HFpEF, but it did not show mortality benefit. Finally, digoxin, which inhibits sodium-potassium-ATPase, was shown to have no role in treating HFpEF in the DIG study. Overall, symptom management and blood pressure control are the goals in HFpEF treatment now. One should also remain vigilant for myocardial ischemia.

IV-76. **The answer is B.** *(Chap. 253)* This patient clearly has adequate cardiac output to maintain peripheral perfusion as evidenced by her physical examination (warm extremities) and adequate blood pressure. However, her elevated creatinine is vexing and indicates that she suffers from cardio-renal syndrome. In some cases, it truly is a depressed cardiac output causing a low glomerular filtration rate (GFR); however, these cases are typically accompanied by other signs of peripheral malperfusion. In most cases when cardiac output is not severely depressed, it is thought that a complex interplay of elevated venous pressures (reducing trans-glomerular perfusion pressures) and abdominal pressures leads to decreased GFR. In these cases, reducing venous pressures with diuretics is the most reasonable first option. In patients who respond poorly (rising creatinine, or adverse hemodynamic effects) to hemodynamic monitoring or ultrafiltration can be considered. Digoxin should be used with caution in renal insufficiency, and it has no real benefit acutely here. In cases where cardiac output is thought to be severely depressed and peripheral perfusion is compromised, inotropic therapy may be indicated.

IV-77. **The answer is E.** *(Chap. 253)* The utility of invasive hemodynamic monitoring during acute decompensated heart failure has been highly scrutinized recently. Based on several observational and randomized trials, the routine use of a pulmonary artery catheter is not recommended and should be restricted to those who respond poorly to diuresis or experience hypotension or signs and symptoms suggestive of a low cardiac output where therapeutic targets are unclear. In this patient with hypotension and signs of low cardiac output, invasive monitoring will allow the clinician to rapidly, objectively assess any changes in hemodynamic status and respond appropriately. In states of “cold” (poor perfusion) and “wet” (elevated filling pressures, or hypervolemia) heart failure, the stroke volume and cardiac output are decreased. Left ventricular stroke work index (a calculated value which normalizes left ventricular work for the patient’s body surface area and afterload) is also diminished. Mixed venous oxygen saturation is greatly diminished as well, as the Fick equation dictates that cardiac output is proportional to the venous oxygen saturation if oxygen consumption and arterial oxygen saturation are normal. Systemic vascular resistance equals the (mean systemic arterial pressure – mean right atrial pressure) divided by cardiac output. As cardiac output drops, the systemic vasculature will increase its resistance to attempt to maintain blood pressure and end-organ perfusion pressure. However, this initially compensatory action becomes deleterious as an inefficient left ventricle must work against an ever-increasing afterload. The most effective inotropic agents in acute decompensated heart failure (milrinone and dobutamine) also have vasodilatory properties to combat this harmful systemic vascular resistance increase.

IV-78. **The answer is E.** *(Chap. 252)* This patient is on optimal doses of the three medications forming the foundation of neurohormonal therapy for heart failure with reduced ejection fraction (HFrEF). Digoxin was shown to reduce hospitalizations, but not mortality in the DIG trial. The addition of valsartan to angiotensin-converting enzyme (ACE) inhibitor therapy was studied in the Val-HEFT trial and showed a trend toward worse outcomes. Similarly, aliskiren (a direct renin inhibitor) was studied in addition to ACE inhibitors in the ASTRONAUT trial and showed no mortality benefit and an abundance of side effects such as hyperkalemia and hypotension. Ivabradine, a novel heart rate reducing agent, was studied in the SHIFT trial and showed mortality benefit, but only in patients with a heart rate >70 beats/min already on beta blockers. This patient’s heart rate is controlled.

IV-79. **The answer is D.** *(Chap. 253)* A routine 12-lead electrocardiogram (ECG) is recommended. The major importance of the ECG is to assess cardiac rhythm and determine the presence of left ventricular (LV) hypertrophy or a prior myocardial infarction (presence or absence of Q waves) as well as to determine QRS width to ascertain whether the patient may benefit from resynchronization therapy. A normal ECG virtually excludes LV systolic dysfunction. Peripheral edema, an elevated or distended jugular vein, and an enlarged and/or pulsatile liver are common in heart failure states.

IV-80. **The answer is D.** *(Chap. 253)* Two-dimensional (2D) echocardiography is used to measure right ventricle (RV) wall thickness and chamber dimensions. The interventricular septum may move paradoxically during systole in the presence of RV pressure overload, highlighting a deleterious interaction between the RV and the left ventricle (LV). Doppler echocardiography can be used to assess pulmonary artery pressures. The location of the RV behind the sternum and its crescent shape can challenge assessment of RV function by echocardiography, especially when parenchymal lung disease is present. Calculated measures of RV function (e.g., tricuspid annular plane systolic excursion, systolic velocity of the RV free wall, strain of the RV free wall, or the Tei Index) supplement more subjective assessments. MRI is also useful for assessing RV structure and function, particularly in patients who are difficult to image with 2D echocardiography because of severe lung disease. Cardiac catheterization confirms the diagnosis of pulmonary hypertension and can exclude elevated left-sided pressures (measured as the pulmonary capillary wedge pressure or the LV end-diastolic pressure) as a cause for right-sided heart failure. B-type natriuretic peptide (BNP) and N-terminal BNP levels are elevated in patients with cor pulmonale secondary to RV myocardial stretch but can be elevated in the left side of the heart.

IV-81. **The answer is B.** *(Chap. 254)* This patient presents with a classic history for fulminant viral myocarditis. A small number of patients present with fulminant myocarditis, with rapid progression from a severe febrile respiratory syndrome to cardiogenic shock that may involve multiple organ systems, leading to renal failure, hepatic failure, and coagulopathy. These patients are typically young adults who have recently been dismissed from urgent care settings with antibiotics for bronchitis or oseltamivir for viral syndromes, only to return within a few days in rapidly progressive cardiogenic shock. Prompt triage is vital to provide aggressive support with high-dose IV catecholamine therapy and sometimes with temporary mechanical circulatory support. Recognition of patients with this fulminant presentation is potentially life-saving as more than half can survive, with marked improvement demonstrable within the first few weeks. The left ventricular function of these patients often recovers to near-normal, although residual diastolic dysfunction may limit vigorous exercise for some survivors. There is no established role for measuring circulating anti-heart antibodies, which may be the result, rather than a cause, of myocardial injury and have been found in patients with coronary artery disease and genetic cardiomyopathy. There is currently no specific therapy recommended during any stage of viral myocarditis. Large trials of immunosuppressive therapy for Dallas Criteria–positive myocarditis have been negative.

IV-82. **The answer is C.** *(Chap. 254)* Giant cell myocarditis accounts for 10–20% of biopsy-positive cases of myocarditis. Giant cell myocarditis typically presents with rapidly progressive heart failure and tachyarrhythmias. Diffuse granulomatous lesions are surrounded by extensive inflammatory infiltrate unlikely to be missed on endomyocardial biopsy, often with extensive eosinophilic infiltration. Associated conditions are thymomas, thyroiditis, pernicious anemia, other autoimmune diseases, and occasionally recent infections. Glucocorticoid therapy is less effective than for sarcoidosis and is sometimes combined with other immunosuppressive agents. The course is generally of rapid deterioration requiring urgent transplantation. Although the severity of presentation and myocardial histology are more fulminant than with sarcoidosis, the occasional finding of giant cell myocarditis after sarcoidosis suggests that they may in some cases represent different stages of the same disease spectrum.

IV-83. **The answer is C.** *(Chap. 254)* Peripartum cardiomyopathy is a rare complication of pregnancy and can occur during the last trimester or within the first 6 months postpartum. Risk factors include advanced age, increased parity, twin pregnancy, malnutrition, use of tocolytic therapy for premature labor, and preeclampsia.

IV-84. **The answer is D.** *(Chap. 254)* Cardiac involvement is common in many of the neuromuscular diseases. The electrocardiogram pattern of Duchenne muscular dystrophy is unique and consists of tall R waves in the right precordial leads with an R/S ratio >1.0, often with deep Q waves in the limb and precordial leads. These patients often have a variety of supraventricular and ventricular arrhythmias and are at risk for sudden death due to the intrinsic cardiomyopathy as well as the low ejection fraction. Implantable cardioverter defibrillators should be considered in the appropriate patient. Global left ventricular dysfunction is a common finding in dilated cardiomyopathies, whereas focal wall motion abnormalities and angina are more common if there is ischemic myocardium. This patient is at risk for venous thromboembolism; however, chronic thromboembolism would not account for the severity of the left heart failure and would present with findings consistent with pulmonary hypertension. Amyotrophic lateral sclerosis is a disease of motor neurons and does not involve the heart. This patient would be atypically young for that diagnosis. An advanced atrial septal defect would present with cyanosis and heart failure (Eisenmenger physiology).

IV-85. **The answer is B.** *(Chap. 254)* There is currently no specific therapy recommended during any stage of viral myocarditis. During acute infection, therapy with anti-inflammatory or immunosuppressive medications is avoided, as their use has been shown to increase viral replication and myocardial injury in animal models. Therapy with specific antiviral agents (such as oseltamivir) has not been studied in relation to cardiac involvement. There is ongoing investigation into the impact of antiviral therapy to treat chronic viral persistence identified from endomyocardial biopsy. Large trials of immunosuppressive therapy for Dallas Criteria–positive myocarditis have been negative. There are some initial encouraging results and ongoing investigations with immunosuppressive therapy for immune-mediated myocarditis defined by immunohistologic criteria on biopsy or circulating anti-heart antibodies in the absence of myocardial viral genomes. However, neither antiviral nor anti-inflammatory therapies are currently recommended. Until there is a better understanding of the phases of viral myocarditis and the effects of targeted therapies, treatment will continue to be guided by general recommendations for dilated cardiomyopathy, which includes an angiotensin-converting enzyme inhibitors.

IV-86. **The answer is E.** *(Chap. 254)* Chagas disease is the third most common parasitic infection in the world and the most common infective cause of cardiomyopathy. The protozoan *Trypanosoma cruzi* is transmitted by the bite of the reduviid bug, endemic in the rural areas of South and Central America. Transmission can also occur through blood transfusion, organ donation, from mother to fetus, and occasionally orally. While programs to eradicate the insect vector have decreased the prevalence from about 16 million to <10 million in South America, cases are increasingly recognized in developed Western countries.

IV-87. **The answer is A.** *(Chap. 254)* Sarcoidosis is a multisystem disease most commonly affecting the lungs. Although classically presenting with higher prevalence in young African American men, the epidemiology appears to be changing, with increasing recognition of sarcoidosis in Caucasian patients in nonurban areas. Patients with pulmonary sarcoid are at high risk for cardiac involvement, but cardiac sarcoidosis also occurs without clinical lung disease. Regional clustering of the disease supports the suspicion that the granulomatous reaction is triggered by an infectious or environmental allergen not yet identified. The sites and density of cardiac granulomata, the time course, and the degree of extracardiac involvement are remarkably variable. Patients may present with rapid-onset heart failure and ventricular tachyarrhythmias, conduction block, chest pain syndromes, or minor cardiac findings in the setting of ocular involvement, an infiltrative skin rash, or a nonspecific febrile illness. They may also present less acutely after months to years of fluctuating cardiac symptoms. When ventricular tachycardia or conduction block dominates the initial presentation of heart failure without coronary artery disease, suspicion should be high for these forms of granulomatous myocarditis. Depending on the time course, the ventricles may appear restrictive or dilated. There is often right ventricular predominance of both dilation and ventricular arrhythmias, sometimes initially attributed to arrhythmogenic right ventricular cardiomyopathy. Small ventricular aneurysms are common. CT of the chest often reveals pulmonary lymphadenopathy even in the absence of clinical lung disease. Metabolic imaging (positron emission tomography) of the whole chest can highlight active sarcoid lesions that are avid for glucose. MRI of the heart can identify areas likely to be inflammatory. To rule out chronic infections, such as tuberculosis or

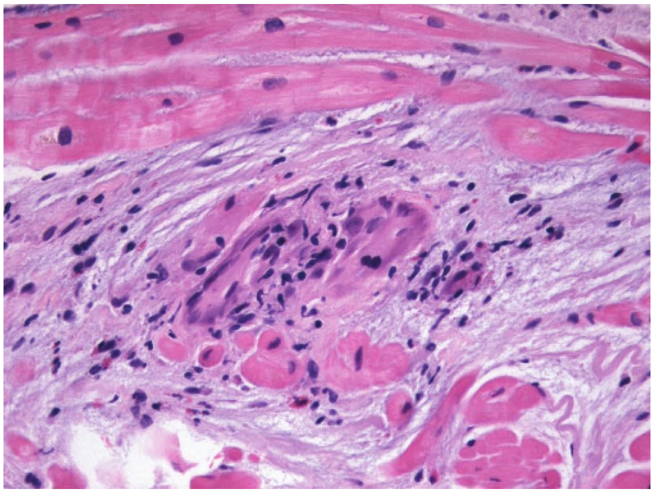


FIGURE IV-87 Used with permission from Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.

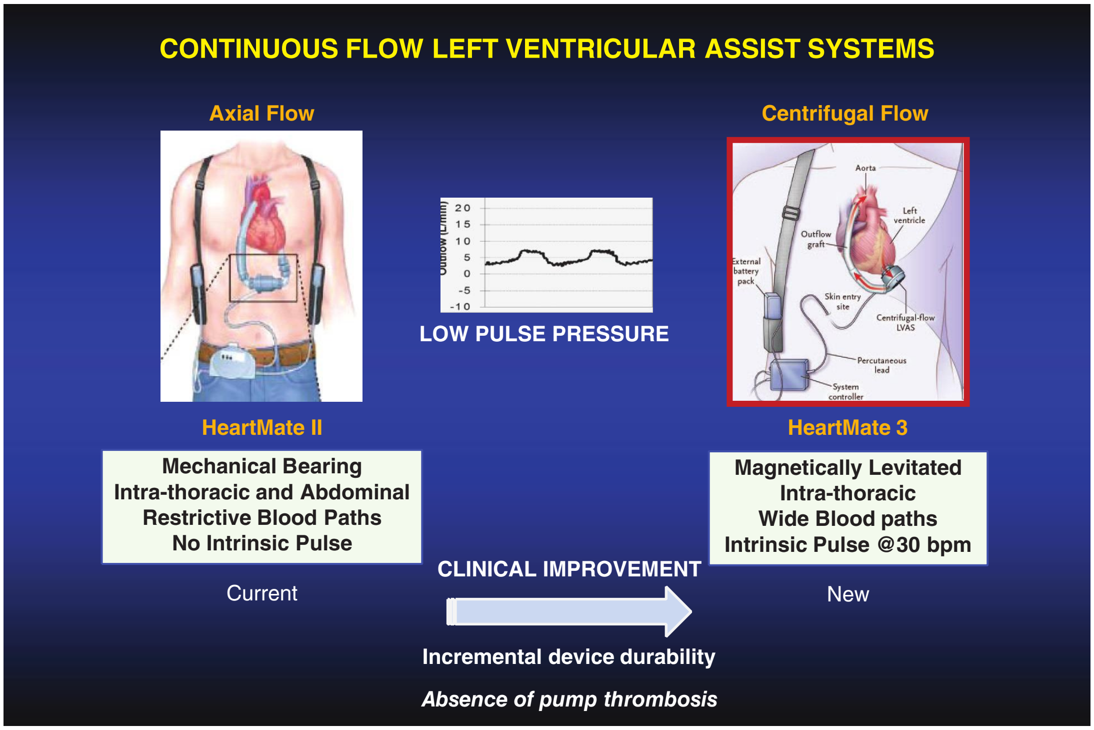
histoplasmosis as the cause of adenopathy, the diagnosis usually requires pathologic confirmation. Biopsy of enlarged mediastinal nodes may provide the highest yield. The scattered granulomas of sarcoidosis (Figure IV-87) can easily be missed on cardiac biopsy.

IV-88. The answer is C. *(Chap. 255)* Despite usually having young donor hearts, cardiac allograft recipients are prone to develop coronary artery disease (CAD). This CAD is generally a diffuse, concentric, and longitudinal process that is quite different from "ordinary" atherosclerotic CAD, which is more focal and often eccentric. The underlying etiology most likely is primarily immunologic injury of the vascular endothelium, but a variety of risk factors influence the existence and progression of CAD, including nonimmunologic factors such as dyslipidemia, diabetes mellitus, and cytomegalovirus infection (as in this patient). It is hoped that newer and improved immunosuppressive modalities will reduce the incidence and impact of these devastating complications, which currently account for the majority of late posttransplantation deaths. Thus far, the immunosuppressive agents mycophenolate mofetil and the mammalian target of the rapamycin inhibitors sirolimus and everolimus have been shown to be associated with short-term lower incidence and extent of coronary intimal thickening; in anecdotal reports, institution of sirolimus was associated with some reversal of CAD. The use of statins also is associated with a reduced incidence of this vasculopathy, and these drugs are now used almost universally in transplant recipients unless contraindicated. Palliation of CAD with percutaneous interventions is probably safe and effective in the short term, although the disease often advances relentlessly. Because of the denervated status of the organ, patients rarely experience angina pectoris, even in advanced stages of disease. Antibody (humoral) mediated rejection is exceedingly rare in a patient this far out from transplant, particularly one who fortunately has had no prior rejection episodes. While cellular rejection is possible, the presence of a normal left ventricle (and no arrhythmias) makes it less likely. Tacrolimus most commonly causes hypertension, neurologic complications, and renal insufficiency. Mycophenolate mofetil most commonly causes bone marrow suppression and diarrhea. Low-dose prednisone is generally well tolerated, though chronic steroids carry incipient risk of diabetes, obesity, skin changes, iatrogenic adrenal insufficiency, osteoporosis, and cataracts. None of these drugs classically causes dyspnea.

IV-89. The answer is D. *(Chap. 255)* For patients with end-stage cardiomyopathy (New York Heart Association class IV, or peak oxygen consumption less than 14 mL/kg per minute), the prognosis is abysmal. In the landmark REMATCH trial, the 2-year survival of the medically treated arm was only 8%. Orthotopic heart transplant is the gold standard therapy for these patients. However, some patients are not candidates due to underlying comorbidities that would render a transplant too dangerous. For these patients, the continuous flow left ventricular assist devices (LVADs) have been shown convincingly to improve mortality (2-year survival in REMATCH was around 60%, and has improved since then). While it is unreasonable to predict a complication-free course (most patients have thrombotic, infectious, or neurologic complications during their course of support), the median survival for patients with LVAD support is now approaching 5 years. Stem cell therapy is currently investigational only, and has never been shown to meaningfully impact survival. Similarly, milrinone or dobutamine therapy (inotropic support) can be used continuously to support quality of life in a palliative goal, or as a bridge to initiation of mechanical support or transplant. However, all studies show that the use of inotropes negatively impacts survival.

IV-90. **The answer is B.** *(Chap. 255)* The most common contemporary cardiac transplant operation is referred to as a "bicaval" orthotopic cardiac transplant that mimics the natural anatomic position. In this operation, the donor and recipient superior and inferior vena cava are connected as are the aortic and pulmonary great vessels. The left atrium of the recipient retains its roof, including the draining pulmonary veins, and the donor left atrium is then sutured to the retained atrial tissue. This technique maintains function of the donor right atrium, which is important for governing early postoperative right heart output, and may prevent atrial arrhythmias.

IV-91. **The answer is B.** *(Chap. 255)* The HeartMate 3 (HM3) is a centrifugal, continuous flow pump that is placed in the thorax and is engineered to be a more hemocompatible left ventricular assist device. This device is constructed with a fully magnetically levitated motor, offers wider blood flow paths, and even exhibits a fixed intrinsic pulse (by the motor ramping its speed up and down at 2-second intervals). There is no valve in the outflow graft in the HM3. The mechanical bearing axial flow HM2 pump is prone to thrombosis, while the frictionless magnetically levitated centrifugal flow HM3 does not induce hemolysis or pump thrombosis (Figure IV-91).



CONTINUOUS FLOW LEFT VENTRICULAR ASSIST SYSTEMS

Axial Flow

Centrifugal Flow

LOW PULSE PRESSURE

HeartMate II

Mechanical Bearing
Intra-thoracic and Abdominal
Restrictive Blood Paths
No Intrinsic Pulse

Current

HeartMate 3

Magnetically Levitated
Intra-thoracic
Wide Blood paths
Intrinsic Pulse @30 bpm

New

CLINICAL IMPROVEMENT

Incremental device durability

Absence of pump thrombosis

FIGURE IV-91 *Abbreviation:* LVAS, left ventricular assist system.

IV-92. The answer is D. *(Chap. 256)* Mr. Belliard is in cardiogenic shock due to his progressive aortic stenosis. The natural history of symptomatic severe aortic stenosis (AS) is not encouraging. Aortic valve area, on average declines by 0.1 cm^2/year, and gradient increases by 7 mmHg annually. The average time to death after the onset of various symptoms is as follows: angina pectoris, 3 years; syncope, 3 years; dyspnea, 2 years; and congestive heart failure, 1.5–2 years. Moreover, in >80% of patients who died with AS, symptoms had existed for <4 years. Currently, Mr. Belliard has compromised organ function due to the severe left ventricle obstruction of AS and resultant low stroke volume. Any negative inotropic or chronotropic agents, such as metoprolol, may prove fatal, as reducing heart rate (HR) or stroke volume will further compromise cardiac output. Digoxin is unlikely to augment stroke volume to any significant degree in the setting of severe AS, and it is risky in the setting of compromised renal function. While statins have been shown to slightly slow the progression of AS, they serve no role in the acute setting. Phenylephrine is an alpha agonist. While it may serve to increase blood pressure, it acts via peripheral vasoconstriction, which further increases the resistance the LV is working against. Percutaneous aortic balloon valvuloplasty (PABV) is a poor long-term therapeutic option as almost all patients have recurrence of severe AS within 6 months to a year. However, PABV can serve as a bridge to definite therapy (such as surgical aortic valve replacement), temporarily improving cardiac output and end-organ perfusion to render surgical risk acceptable. Other options would be an intra-aortic balloon pump, or in rare cases mechanical circulatory support.

IV-93. The answer is D. *(Chap. 256)* Mrs. Treadwell has evidence of the clinical entity "low gradient, low flow aortic stenosis." Conceptually, the aortic valve area during systole is dependent on two factors: (1) aortic valve morphology (e.g., calcific aortic stenosis [AS] with restricted leaflet motion) and (2) ventricular contractile force. Even a normal aortic valve will open very little if the ventricle contracts very weakly. As in Mrs. Treadwell's case, the finding of a low calculated aortic valve area without a severely high gradient (severe is >40 mmHg) in the setting of reduced left ventricular function defines the entity of low gradient, low flow AS. It is difficult to determine whether the valve area is low due to above factor 1 or 2 during a resting echocardiography. However, dobutamine stress will accomplish two goals. First, it will assess for ventricular viability (the ability to increase stroke volume by 20%), which is shown to predict outcomes after aortic valve replacement. Second, and more importantly, as the ventricular contractility increases, it allows the clinician to differentiate between true, morphologic AS and the appearance of AS due to compromised ventricular function (termed pseudo-aortic stenosis). While the other options may aid in other facets of this patient's management, none will allow the clinician to make this differentiation.

IV-94. The answer is C. *(Chap. 256)* A bicuspid aortic valve (BAV) is the most common congenital heart valve defect and occurs in 0.5–1.4% of the population with a 2–4:1 male-to-female predominance. The inheritance pattern appears to be autosomal dominant with incomplete penetrance, although some have questioned an X-linked component as suggested by the prevalence of BAV disease among patients with Turner syndrome. The prevalence of BAV disease among first-degree relatives of an affected individual is ~10%. A single gene defect to explain the majority of cases has not been identified, although a mutation in the *NOTCH1* gene has been described in some families. Abnormalities in endothelial nitric oxide synthase and NKX2.5 have been implicated as well. Medial degeneration with ascending aortic aneurysm formation occurs commonly among patients with BAV disease; aortic coarctation is less frequently encountered. Patients with BAV disease have larger aortas than patients with comparable tricuspid aortic valve disease. The aortopathy develops independently of the hemodynamic severity of the valve lesion, but directional shear forces dictated by the anatomic configuration of the valve may influence its expression.

IV-95. The answer is A. *(Chap. 255)* A delayed and weak carotid pulse is typical in cases of severe aortic stenosis. The carotid arterial pulse rises slowly to a delayed peak (pulsus parvus et tardus). In the late stages, when stroke volume declines the systolic pressure may fall and the pulse pressure will narrow. Augmentation of the murmur with Valsalva (left ventricular preload reduction) occurs in hypertrophic cardiomyopathy with outflow tract obstruction. Bounding femoral pulse is commonly felt in aortic regurgitation. Option D describes the murmur of mitral regurgitation, whereas option E might be a heart with a ventricular aneurysm or ventricular septal defect.

IV-96. **The answer is A.** *(Chap. 257)* An increase in the left ventricle (LV) end-diastolic volume (increased preload) constitutes the major hemodynamic compensation for aortic regurgitation (AR), thus preload is increased. The total LV stroke volume also increases to attempt to maintain effective LV stroke volume (total LV stroke volume – regurgitant volume). To do this, the LV must dilate. As the LV dilates, the wall tension to develop a given systolic blood pressure must increase as dictated by Laplace's law, and thus afterload is increased. During diastole, as a large volume of blood leaves the systemic circulation to regurgitate into the LV, the diastolic pressure falls, often equilibrating with the LV pressure in severe cases. Coronary perfusion occurs primarily during diastole and depends on the gradient between aortic pressure and LV pressure through the coronaries. This explains why patients with severe AR may manifest anginal symptoms.

IV-97. **The answer is C.** *(Chap. 257)* This patient has severe, acute aortic regurgitation and indeed warrants emergent surgery. Note that her murmur is very quiet and short. In the setting of acute, severe valvular regurgitant lesions, the pressure gradient between the two chambers (in this case the aorta and left ventricle) quickly equilibrates during the regurgitant period. Sometimes patients with these lesions can have no audible murmur at all, making diagnosis challenging. In this case, the goal is to reduce the regurgitant volume and thus increase effective stroke volume (total stroke volume – regurgitant volume). Interventions that increase systemic vascular resistance (vasopressin or norepinephrine) will increase regurgitant volume. Likewise, since aortic regurgitation occurs during diastole, interventions that increase diastolic time (e.g., beta blockers) will also worsen regurgitant volume. Since intra-aortic balloon pumps inflate during diastole, they will also worsen regurgitation from aortic to left ventricle and are contraindicated in moderate or worse aortic regurgitation. Nitroprusside will reduce systemic vascular resistance, and thus reduce the driving pressure for regurgitation. Careful administration of nitroprusside, often with concomitant invasive hemodynamic monitoring, may stabilize organ perfusion and allow surgical correction. It is important to realize that no medical therapy will correct this abnormality—surgical correction is the only definitive therapy.

IV-98. **The answer is C.** *(Chap. 257)* Aortic regurgitation (AR) carries some of the odder and more memorable physical examination findings of any valvular disease. A rapidly rising "water-hammer" pulse, which collapses suddenly as arterial pressure falls rapidly during late systole and diastole (Corrigan pulse), and capillary pulsations, an alternate flushing and paling of the skin at the root of the nail while pressure is applied to the tip of the nail (Quincke pulse), are characteristic of chronic severe AR. A booming "pistol-shot" sound can be heard over the femoral arteries (Traube sign), and a to-and-fro murmur (Duroziez sign) is audible if the femoral artery is lightly compressed with a stethoscope. Option C describes the murmur of aortic stenosis.

IV-99. **The answer is B.** *(Chap. 258)* In mitral stenosis, the flow obstruction between the left ventricle and left atrium creates elevated left atrial pressure to maintain cardiac output. For example, once the effective mitral valve orifice reaches 1.5 cm^2, the left atrial pressure must be >25 mmHg to maintain a normal cardiac output. Left ventricular preload, diameter, and end-diastolic pressure are normal or diminished in mitral stenosis. Similarly, cardiac output is normal or diminished. Due to elevated left atrial pressures, pulmonary venous pressures rise. This causes pulmonary vascular congestion and distention, and it reduces pulmonary vascular compliance.

IV-100. **The answer is D.** *(Chap. 258)* The left atrial to left ventricular pressure gradient is highly dependent on heart rate since diastolic duration is inversely related to heart rate. In the setting of mitral stenosis, a long diastolic time allows more time for the left atrium to empty, and thus lower pressures. Hence, sinus bradycardia is advantageous in the setting of mitral stenosis, and inducing a faster heart rate via pacemaker would be harmful. The loss of atrial systole during atrial fibrillation is often poorly tolerated in mitral stenosis, and regaining sinus rhythm would undoubtedly lower atrial pressure. However, the vast majority of patients with mitral stenosis are unable to maintain sinus rhythm long term as their atria tend to be very dilated. Diuretics and percutaneous mitral valvotomy will lower left atrial pressure.

IV-101. **The answer is C.** *(Chap. 258)* Rheumatic fever is the leading cause of mitral stenosis (MS). Other less common etiologies of obstruction to left ventricular inflow include congenital mitral valve stenosis, cor triatriatum, mitral annular calcification with extension onto the leaflets, systemic lupus erythematosus, rheumatoid arthritis, left atrial myxoma, and infective endocarditis with large vegetations. Pure or predominant MS occurs in ~40% of all patients with rheumatic heart disease and a history of rheumatic fever. In other patients with rheumatic heart disease, lesser degrees of MS may accompany mitral regurgitation and aortic valve disease. With reductions in the incidence of acute rheumatic fever, particularly in temperate climates and developed countries, the incidence of MS has declined considerably over the past several decades. However, it remains a major problem in developing nations, especially in tropical and semitropical climates.

IV-102. **The answer is A.** *(Chap. 258)* The physiology of mitral stenosis leads to a high symptom dependence on heart rate and metabolic demands. As the heart rate climbs with exercise, diastolic filling time declines. Thus, transit time for blood to flow across the stenosed mitral valve is reduced and both left atrial pressure and mitral valve gradient increase. As left atrial pressure rises, so do “upstream” pressures such as the pulmonary artery pressure. As the left atrial and pulmonary artery pressures rise and the pulmonary vasculature is increasingly distended, both pulsatile and nonpulsatile pulmonary vascular resistance load rises.

IV-103. **The answer is A.** *(Chap. 259)* Chronic mitral regurgitation (MR) can result from several disease processes. Distinction should be drawn between primary MR, in which the leaflets and/or chordae tendineae are primarily responsible for abnormal valve function, and secondary (functional) MR, in which the leaflets and chordae tendineae are usually normal but the regurgitation is caused by left ventricular remodeling with annular enlargement, papillary muscle displacement, leaflet tethering, or their combination. Patient assessment, treatment approach, and long-term prognosis differ significantly between primary and secondary MR.

IV-104. **The answer is C.** *(Chap. 259)* The resistance to left ventricular (LV) emptying (LV afterload) is reduced in patients with mitral regurgitation (MR). As a consequence, the LV is decompressed into the left atrium (LA) during ejection, and with the reduction in LV size during systole, there is a rapid decline in LV tension. The initial compensation to MR is more complete LV emptying. However, LV volume increases progressively with time as the severity of the regurgitation increases and as LV contractile function deteriorates. This increase in LV volume is often accompanied by a reduced forward cardiac output. LV compliance is often increased, and thus, LV diastolic pressure does not increase until late in the course. The regurgitant volume varies directly with the LV systolic pressure and the size of the regurgitant orifice; the latter, in turn, is influenced by the extent of LV and mitral annular dilation. Because the ejection fraction rises in severe MR in the presence of normal LV function, even a modest reduction in this parameter (<60%) reflects significant contractile dysfunction.

IV-105. **The answer is C.** *(Chap. 259)* Surgery for chronic severe primary mitral regurgitation (MR) is indicated once symptoms occur. Valve repair is preferred over valve replacement, when feasible. Surgery should also be recommended for asymptomatic patients with left ventricular (LV) dysfunction characterized by an ejection fraction (EF) <60% or an LV end-systolic dimension (LV ESD) >40 mm. Other indications for early consideration of mitral valve repair in asymptomatic patients include (1) recent-onset atrial fibrillation (duration <3 months), (2) pulmonary hypertension (defined as a systolic pulmonary artery pressure ≥50 mmHg at rest or ≥60 mmHg with exercise), and (3) a progressive decrease in LV EF or increase in LV ESD on serial imaging. These aggressive recommendations for surgery are predicated on the adverse long-term consequences of waiting for LV function to decline further as well as the outstanding results achievable with mitral valve repair by reference surgeons at high-volume centers. Indeed, repair of myxomatous MR (e.g., prolapse, flail) in patients <75 years with normal LV systolic function and no coronary artery disease can now be performed by experienced surgeons with <1% perioperative mortality risk. In contrast to the acute setting, there are no large, long-term prospective studies to substantiate the use of vasodilators for the treatment of chronic, isolated severe MR with preserved LV systolic function in the absence of systemic hypertension.

IV-106. The answer is A. *(Chap. 260)* In most patients with mitral valve prolapse (MVP), the cause is unknown, but in some, it appears to be genetically determined. A reduction in the production of type III collagen has been incriminated, and electron microscopy has revealed fragmentation of collagen fibrils. MVP is a frequent finding in patients with heritable disorders of connective tissue, including Marfan syndrome, osteogenesis imperfecta, and Ehlers-Danlos syndrome. The posterior mitral leaflet is usually more affected than the anterior, and the mitral valve annulus is often dilated. MVP is more common in women and occurs most frequently between the ages of 15 and 30 years; the clinical course is most often benign. A frequent physical examination finding is the mid or late (nonejection) systolic click, which occurs 0.14 seconds or more after S_1 and is thought to be generated by the sudden tensing of slack, elongated chordae tendineae or by the prolapsing mitral leaflet when it reaches its maximal excursion. Systolic clicks may be multiple and may be followed by a high-pitched, mid-late systolic crescendo-decrescendo murmur, which occasionally is “whooping” or “honking” and is heard best at the apex. Radiation of the murmur will depend on the involved leaflet. With posterior leaflet prolapse, the jet of mitral regurgitation (MR) is directed anteriorly and the murmur will radiate to the base of the heart. With anterior leaflet involvement, the jet of MR is directed posteriorly and the murmur will radiate to the axilla and back. The click and murmur occur earlier with standing, during the strain phase of the Valsalva maneuver, and with any intervention that decreases left ventricular (LV) volume (preload), exaggerating the propensity of mitral leaflet prolapse. Conversely, squatting and isometric exercises, which increase LV volume, diminish MVP; the click-murmur complex is delayed, moves away from S_1, and may even disappear.

IV-107. The answer is A. *(Chap. 261)* This patient has severe tricuspid regurgitation (TR) secondary to right ventricular dilation and dysfunction, which is in turn secondary to her severe pulmonary arterial hypertension. In cases of functional TR, repair is relegated to instances where surgery is already being pursued for left-sided valvular lesions. Furthermore, the presence of severe pulmonary hypertension is a relative contraindication for TR repair. The right ventricle suddenly finds itself without the “pop-off valve” of severe TR and often fails when faced with the overwhelming afterload of the pulmonary vasculature. Percutaneous tricuspid valve repair is not currently done in clinical practice. Balloon valvotomy is a repair for tricuspid stenosis, not regurgitation. Initial treatment for her pulmonary hypertension should include diuretics and salt restriction to reduce preload along with approved therapy for pulmonary arterial hypertension.

IV-108. The answer is C. *(Chap. 262)* Pulmonic valve stenosis (PS) is essentially a congenital disorder. With isolated PS, the valve is typically domed. Dysplastic pulmonic valves are seen as part of Noonan syndrome, which maps to chromosome 12. Mutations in the *PTPN1* gene are associated with about half of all cases of Noonan syndrome. Much less common etiologies include carcinoid and obstructing tumors or bulky vegetations. The pulmonic valve is only very rarely affected by the rheumatic process.

IV-109. The answer is D. *(Chap. 262)* The physical examination hallmark of pulmonic regurgitation (PR) is a high-pitched, decrescendo diastolic murmur (Graham Steell murmur) heard along the left sternal border that can be difficult to distinguish from the more frequently appreciated murmur of aortic regurgitation (AR). The Graham Steell murmur may become louder with inspiration and is usually associated with a loud and sometimes palpable P_2 and a right ventricular lift, as would be expected in patients with significant pulmonary arterial hypertension of any cause. Bounding peripheral pulses and wide systemic pulse pressure are seen with AR and not pulmonic regurgitation.

IV-110. The answer is D. *(Chap. 263)* This patient is in a precarious situation and likely will require emergent surgical intervention to survive. The combination of severe obstruction to left ventricular (LV) outflow (severe aortic stenosis) and acute, severe regurgitant mitral valve disorder will inevitably lead to intractable pulmonary edema and cardiogenic shock unless both structural abnormalities are corrected. At the advent of severe mitral regurgitation, the LV will be more effectively "unloaded" as now it can eject not only against the stenosed aortic valve, but also into the relatively low pressure left atrium, thus afterload will decline. Likewise, with more of the stroke volume going ineffectively into the left atrium, the effective stroke volume (total stroke volume – regurgitant volume) will decline. The aortic valve gradient will decline merely because there is less volume going across the aortic valve with each contraction. Likewise, since both catheter-derived and echocardiographic-derived calculations of aortic valve area are dependent on the gradient for calculation, they will decline. Ejection fraction (EF), however, will increase as the LV will be better able to contract in the state of relatively lower afterload. This highlights a misconception that higher EF is "always better." Left ventricular EF is highly dependent not only on the contractile state of the ventricle, but also on its afterload state.

IV-111. The answer is D. *(Chap. 263)* In patients with mixed aortic stenosis (AS) and aortic regurgitation (AR), assessment of valve stenosis can be influenced by the magnitude of the regurgitant valve flow. Because transvalvular systolic flow velocities are augmented in patients with AR and preserved left ventricular (LV) systolic function, the LV-aortic Doppler–derived pressure gradient and the intensity of the systolic murmur will be elevated to values higher than expected for the true systolic valve orifice size as delineated by planimetry. Uncorrected, the Gorlin formula, which relies on forward cardiac output (systolic transvalvular flow) and the mean pressure gradient for calculation of valve area, is not accurate in the setting of mixed aortic valve disease.

IV-112. The answer is D. *(Chap. 264)* The four classic components of the tetralogy of Fallot are malaligned ventricular septal defect (VSD), obstruction to right ventricular (RV) outflow, aortic override of the VSD, and RV hypertrophy (due to the RV's response to aortic pressure via the large VSD). Tricuspid atresia is associated with Ebstein anomaly and hypoplastic right heart syndrome. In these cases a concurrent systemic-to-pulmonary connection is required to maintain early life (such as a patent ductus arteriosus). Right heart bypass operations such as the Glenn shunt or Fontan palliation can provide adequate pulmonary flow to support patients into and through early adulthood.

IV-113. The answer is D. *(Chap. 264)* This patient has a small muscular ventricular septal defect (VSD). The decision to treat a VSD is complex, but it is based on the principle of avoiding any right ventricular and pulmonary vascular compromise. Similarly, one must avoid repairing a VSD in the setting of overt pulmonary hypertension, as this is clearly associated with worse outcomes. Closure is not recommended for patients with normal pulmonary arterial pressures with small shunts (pulmonary-to-systemic flow ratios of <1.5:1). Operative correction or transcatheter closure is indicated when there is a moderate to large left-to-right shunt with a pulmonary-to-systemic flow ratio >1.5:1, in the absence of prohibitively high levels of pulmonary vascular resistance (pulmonary arterial resistance is less than two-thirds of systemic arterial resistance). This patient has a normal pulmonary artery pressure, a pulmonary vascular resistance to systemic vascular resistance ratio of 0.33, and Qp:Qs of 1.25, therefore closure is not warranted at this time, but consistent follow-up is indicated.

IV-114. The answer is B. *(Chap. 264)* The most common birth defects are cardiovascular in origin. These malformations are due to complex multifactorial genetic and environmental causes. Recognized chromosomal aberrations and mutations of single genes account for <10% of all cardiac malformations. Congenital heart disease (CHD) complicates ~1% of all live births in the general population—about 40,000 births per year—but occurs more frequently in the offspring (about 4–10%, depending on maternal CHD type) of women with CHD. Because of the remarkable surgical advances over the last 60 years, >90% of afflicted neonates and children now reach adulthood; women with CHD may now frequently successfully bear children after competent repairs. As such, the population with CHD is steadily increasing.

Women with CHD are at increased risk for peripartum and postpartum complications, but maternal CHD is generally not considered an absolute contraindication to pregnancy unless the mother has certain high-risk features (e.g., cyanosis, pulmonary hypertension, decompensated heart failure, arrhythmias, and aortic aneurysm, among others).

IV-115. **The answer is D.** *(Chap. 264)* Atrial septal defect (ASD) is a common cardiac anomaly that may be first encountered in adults and occurs more frequently in females. Sinus venosus ASD occurs high in the atrial septum near the entry of the superior vena cava into the right atrium and is associated frequently with anomalous pulmonary venous connection from the right lung to the superior vena cava or right atrium. Ostium primum ASDs lie adjacent to the atrioventricular valves, either of which may be deformed and regurgitant. Ostium primum ASDs are common in Down syndrome, often as part of complex atrioventricular septal defects with a common atrioventricular valve and a posterior defect of the basal portion of the interventricular septum. The most common ostium secundum ASD involves the fossa ovalis and is mid-septal in location; this should not be confused with a patent foramen ovale (which is present in ~25% of healthy adults). Anatomic obliteration of the foramen ovale ordinarily follows its functional closure soon after birth, but residual "probe patency" is a common normal variant; ASD denotes a true deficiency of the atrial septum and implies functional and anatomic patency.

IV-116. **The answer is C.** *(Chap. 264)* Table IV-116 summarized the categories of risk for varying congenital or acquired cardiovascular disease during pregnancy. Note that severe native aortic coarctation is World Health Organization (WHO) IV (pregnancy contraindicated).

TABLE IV-116 **Modified WHO Classification of Heart Disease in Pregnancy**

WHO I
• Uncomplicated, small or mild pulmonary stenosis, patent ductus arteriosus, mitral valve prolapse
• Successfully repaired simple lesions (atrial or ventricular septal defect, patent ductus arteriosus, partially anomalous pulmonary venous drainage)
• Isolated atrial or ventricular ectopic beats
WHO II (if otherwise well and uncomplicated)
• Unoperated atrial or ventricular septal defect
• Repaired tetralogy of Fallot
• Most arrhythmias
WHO II–III (depending on individual)
• Mild left ventricular impairment
• Hypertrophic cardiomyopathy
• Native or tissue valvular heart disease not considered WHO I or IV
• Marfan syndrome without aortic dissection
• Aorta <45 mm in bicuspid aortic valve
• Repaired coarctation
WHO III
• Mechanical valve
• Systemic right ventricle
• Fontan circulation
• Cyanotic heart disease (unrepaired)
• Other complex congenital heart disease
• Aortic dilation 40–45 mm in Marfan syndrome
• Aortic dilation 45–50 mm in bicuspid aortic valve
WHO IV (pregnancy contraindicated)
• Pulmonary arterial hypertension
• Severe systemic ventricular dysfunction (LVEF <30%, NYHA class >II)
• Previous peripartum cardiomyopathy with any residual impairment of left ventricular function
• Severe mitral stenosis, severe symptomatic aortic stenosis
• Marfan syndrome with aorta dilated >45 mm
• Aortic dilation >50 mm in bicuspid aortic valve
• Native severe aortic coarctation

Abbreviations: LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; WHO, World Health Organization.

IV-117. The answer is C. *(Chap. 264)* While at first counterintuitive, the left-to-right ventricular shunt with a ventricular septal defect causes *left* ventricular dilation. A good rule of thumb is that intracardiac shunts or intravascular passages that occur below the level of the tricuspid valve result in left heart dilation. Those that occur above the level of the tricuspid valve (atrial septal defect, anomalous pulmonary venous return) cause right ventricular dilation. Patent ductus arteriosus can also cause left ventricular dilation.

IV-118. The answer is B. *(Chap. 265)* The electrocardiogram (ECG) shows diffuse ST elevations with PR depressions. This patient has a classic case of acute pericarditis, likely secondary due to a recent viral infection. His description of the chest pain (positional, pleuritic), auscultatory examination revealing a classic three-component friction rub, typical ECG, and negative cardiac biomarkers are all suggestive of acute pericarditis. There is no specific therapy for acute idiopathic pericarditis, but bedrest and anti-inflammatory treatment with aspirin (2–4 g/d), with gastric protection (e.g., omeprazole 20 mg/d), may be given. If this is ineffective, one of the nonsteroidal anti-inflammatory drugs, such as ibuprofen (400–600 mg tid) or indomethacin (25–50 mg tid) may be tried. In responsive patients, these doses should be continued for 1–2 weeks and then tapered over several weeks. In addition, colchicine (0.5 mg bid, given for 4–8 weeks) has been found to be effective, not only in acute pericarditis, but also in reducing the risk of recurrent pericarditis. Colchicine is concentrated in and interferes with the migration of neutrophils, is contraindicated in patients with hepatic or renal dysfunction, and may cause diarrhea and other gastrointestinal side effects. Glucocorticoids (e.g., prednisone 1 mg/kg per day) usually suppress the clinical manifestations of acute pericarditis in patients who have failed therapy with the anti-inflammatory therapies described above, but they appear to increase the risk of subsequent recurrence. Therefore, full-dose corticosteroids should be given for only 2–4 days and then tapered. Anticoagulants should be avoided because their use could cause bleeding into the pericardial cavity and tamponade.

IV-119. The answer is D. *(Chap. 265)* This patient's presentation and physical examination are most consistent with the diagnosis of constrictive pericarditis. The most common cause of constrictive pericarditis worldwide is tuberculosis, but given the low incidence of tuberculosis in the United States, constrictive pericarditis is a rare condition in this country. With the increasing ability to cure Hodgkin disease with mediastinal irradiation, many cases of constrictive pericarditis in the United States are in patients who received curative radiation therapy 10–20 years prior. These patients are also at risk for premature coronary artery disease. Risks for these complications include the dose of radiation and radiation windows that include the heart. Other rare causes of constrictive pericarditis are recurrent acute pericarditis, hemorrhagic pericarditis, prior cardiac surgery, mediastinal irradiation, chronic infection, and neoplastic disease. Physiologically, constrictive pericarditis is characterized by the inability of the ventricles to fill because of the noncompliant limiting pericardium. In early diastole, the ventricles fill rapidly, but filling stops abruptly when the elastic limit of the pericardium is reached. Clinically, patients present with generalized malaise, cachexia, and anasarca. Exertional dyspnea is common, and orthopnea is generally mild. Ascites and hepatomegaly occur because of increased venous pressure. In rare cases, cirrhosis may develop from chronic congestive hepatopathy. The jugular venous pressure is elevated, and the neck veins fail to collapse on inspiration (Kussmaul sign). Heart sounds may be muffled. A pericardial knock is frequently heard. This is a third heart sound that occurs 0.09–0.12 seconds after aortic valve closure at the cardiac apex. Right heart catheterization would show the "square root sign" characterized by an abrupt y-descent followed by a gradual rise in ventricular pressure. This finding, however, is not pathognomonic of constrictive pericarditis and can be seen in restrictive cardiomyopathy of any cause. Echocardiogram shows a thickened pericardium, dilatation of the inferior vena cava and hepatic veins, and an abrupt cessation of ventricular filling in early diastole. Pericardial resection is the only definitive treatment of constrictive pericarditis. Diuresis and sodium restriction are useful in managing volume status preoperatively, and paracentesis may be necessary. Operative mortality ranges from 5–10%. Underlying cardiac function is normal; thus, cardiac transplantation is not indicated. Pericardiocentesis is indicated for diagnostic removal of pericardial fluid and cardiac tamponade, which is not present on the patient's echocardiogram. Mitral valve stenosis may present similarly with anasarca, congestive hepatic failure, and ascites. However, pulmonary edema and pleural effusions are also common. Examination would be expected to demonstrate a diastolic murmur, and echocardiogram should show a normal pericardium and a thickened immobile mitral valve. Mitral valve replacement would be indicated if mitral stenosis were the cause of the patient's symptoms.

IV-120. **The answer is E.** *(Chap. 265)* This patient has pericardial tamponade. The classic presentation of quiet heart sounds, distended jugular veins, and hypotension are all consistent and typical. In this patient, the pericardial effusion may be neoplastic given his known adenocarcinoma. In pericardial tamponade, the intrapericardial volume rises due to a gathering effusion. At a certain volume (determined by the pericardial compliance and the tempo with which the effusion gathers) pressure rises quickly and will begin to compress cardiac chambers and impede filling. Thus, as intrapericardial pressure increases, intracardiac chamber pressure will also increase, while volumes decline. The elevated jugular venous pressure is a reflection of elevated right atrial pressure.

IV-121. **The answer is D.** *(Chap. 266)* Cardiac tumors can be broadly classified into those that arise primarily in the heart and those that reflect metastatic disease from a distant primary source. Primary cardiac tumors can be further divided into those that are pathologically benign and those that are malignant. Overall, primary cardiac tumors are relatively uncommon, whereas secondary involvement of the heart or pericardium occurs in as many as 20% of patients with end-stage metastatic cancer. Approximately three-quarters of primary cardiac tumors are histologically benign, and the majority of these tumors are myxomas. These tumors may require resection to avoid cardiac or hemodynamic dysfunction with growth, and it is usually curative. Malignant tumors, almost all of which are sarcomas, account for 25% of primary cardiac tumors. Tumors metastatic to the heart are much more common than primary tumors, and their incidence is likely to increase as the life expectancy of patients with various forms of malignant neoplasms is extended by more effective therapy and improved imaging modalities that allow earlier identification of metastatic disease. Although cardiac metastases may occur with any tumor type, the relative incidence is especially high in malignant melanoma and, to a somewhat lesser extent, leukemia and lymphoma. In absolute terms, the most common primary sites from which cardiac metastases originate are carcinoma of the breast and lung, reflecting the high incidence of those cancers.

IV-122. **The answer is C.** *(Chap. 266)* This patient has an atrial myxoma. Myxomas are the most common type of primary cardiac tumor in adults, accounting for one-third to one-half of all cases at postmortem examination, and approximately three-quarters of the tumors treated surgically. They occur at all ages, most commonly in the third through sixth decades, with a female predilection. Approximately 90% of myxomas are sporadic; the remainder are familial with autosomal dominant transmission. Surgical resection of myxomas is always the treatment of choice and nearly always curative. Given the potential for familial disease, echocardiographic screening of first-degree relatives is appropriate, particularly if the patient is young and has multiple tumors or features of a myxoma syndrome.

IV-123. **The answer is E.** *(Chap. 267)* The normal coronary circulation is dominated and controlled by the heart's requirements for oxygen. This need is met by the ability of the coronary vascular bed to vary its resistance (and, therefore, blood flow) considerably while the myocardium extracts a high and relatively fixed percentage of oxygen. Normally, intramyocardial resistance vessels demonstrate a great capacity for dilation. For example, the changing oxygen needs of the heart with exercise and emotional stress affect coronary vascular resistance and in this manner regulate the supply of oxygen and substrate to the myocardium. The epicardial coronary arteries, in the normal state, provide only trivial resistance to flow. Myocardial oxygen extraction is relatively fixed. During tachycardia, the diastolic time period is shortened relative to the systolic.

IV-124. The answer is B. *(Chap. 267)* A wide range of abnormalities in cell metabolism, function, and structure underlie these mechanical disturbances during ischemia. The normal myocardium metabolizes fatty acids and glucose to carbon dioxide and water. With severe oxygen deprivation, fatty acids cannot be oxidized, and glucose is converted to lactate; intracellular pH is reduced, as are the myocardial stores of high-energy phosphates, i.e., adenosine triphosphate and creatine phosphate. Impaired cell membrane function leads to the leakage of potassium and the uptake of sodium by myocytes as well as an increase in cytosolic calcium.

IV-125. The answer is B. *(Chap. 267)* Many patients report a fixed threshold for angina, which occurs predictably at a certain level of activity, such as climbing two flights of stairs at a normal pace. In these patients, coronary stenosis and myocardial oxygen supply are fixed, and ischemia is precipitated by an increase in myocardial oxygen demand; they are said to have stable exertional angina. Angina can be classified by the Canadian Cardiovascular Society Function class as shown in Table IV-125.

TABLE IV-125 Cardiovascular Disease Classification Chart

Class	New York Heart Association Functional Classification	Canadian Cardiovascular Society Functional Classification
I	Patients have cardiac disease but *without* the resulting *limitations* of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	Ordinary physical activity, such as walking and climbing stairs, *does not cause angina.* Angina present with strenuous or rapid or prolonged exertion at work or recreation.
II	Patients have cardiac disease resulting in *slight limitation* of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	*Slight limitation* of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold, or when under emotional stress or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of stairs at a normal pace and in normal conditions.
III	Patients have cardiac disease resulting in *marked limitation* of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.	*Marked limitation* of ordinary physical activity. Walking one to two blocks on the level and climbing one flight of stairs in normal conditions.
IV	Patients have cardiac disease resulting in *inability* to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	*Inability* to carry on any physical activity without discomfort—anginal syndrome *may* be present at rest.

Source: Modified with permission from Goldman L et al: Comparative reproducibility and validity of systems for assessing cardiovascular functional class: advantages of a new specific activity scale. *Circulation* 64:1227, 1981.

IV-126. The answer is B. *(Chap. 267)* Myocardial ischemia also can occur if myocardial oxygen demands are markedly increased and particularly when coronary blood flow may be limited, as occurs in severe left ventricular hypertrophy due to aortic stenosis. The latter can present with angina that is indistinguishable from that caused by coronary atherosclerosis largely due to subendocardial ischemia.

IV-127. The answer is C. *(Chap. 267)* This patient has classic stable angina. Clinical trials have confirmed that with the initial diagnosis of stable ischemic heart disease, it is first appropriate to initiate a medical regimen as described. Revascularization should be considered in the presence of unstable phases of the disease, intractable symptoms, severe ischemia or high-risk coronary anatomy, diabetes, and impaired left ventricular function. Revascularization should be employed in conjunction with, but not replace, the continuing need to modify risk factors and assess medical therapy.

IV-128. The answer is A. *(Chap. 268)* The diagnosis of acute coronary syndrome is based largely on the clinical presentation. Typically, chest discomfort is severe and has at least one of three features: (1) it occurs at rest (or with minimal exertion), lasting >10 minutes; (2) it is of relatively recent onset (i.e., within the prior 2 weeks); and/or (3) it occurs with a crescendo pattern (i.e., distinctly more severe, prolonged, or frequent than previous episodes). The diagnosis of non–ST-elevation myocardial infarction (NSTEMI) is established if a patient with these clinical features develops evidence of myocardial necrosis, as reflected in abnormally elevated levels of biomarkers of cardiac necrosis. Given the electrocardiogram without ST elevations, this patient does not have NSTEMI. Also, this clinical presentation of accelerating angina, now occurring at rest, obviates stable angina. However, since this patient does not yet have cardiac biomarker results, one cannot differentiate between unstable angina and NSTEMI. Further information is needed.

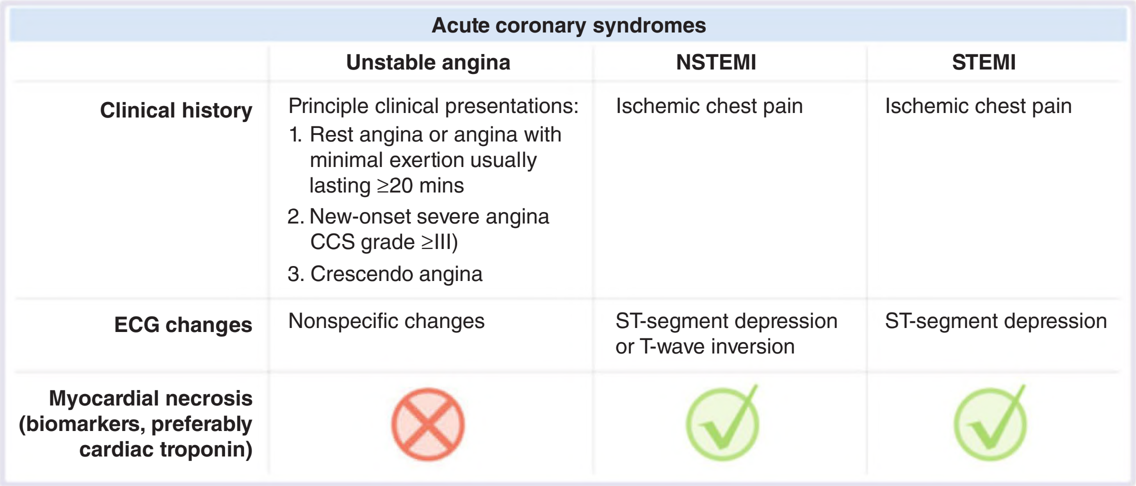
IV-129. The answer is E. *(Chap. 268)* It is important to remember that while cardiac troponin biomarkers (troponin I or troponin T) are quite sensitive for myocardial infarction due to coronary occlusion, they lack somewhat in specificity. In patients without a clear clinical history of myocardial ischemia, minor cardiac troponin elevations have been reported and can be caused by congestive heart failure, myocarditis, or pulmonary embolism, or using high sensitivity assays, they may occur in ostensibly normal subjects. Thus, in patients with an unclear history, small elevations of cardiac troponin, especially if they are persistent, may not be diagnostic of an acute coronary syndrome. In this patient, the troponin elevation is likely due to his hypertensive urgency brought on by missed hemodialysis and volume overload. Treating the proximal cause will help him. It would be prudent to continue to trend cardiac biomarkers and electrocardiograms over time as well.

IV-130. The answer is E. *(Chap. 268)* This patient is suffering from a non–ST-elevation myocardial infarction (NSTEMI). The two cornerstones of pharmacologic therapy in NSTEMI management are reduction of myocardial oxygen demand and antithrombotic therapy targeted at a presumed partially occluding thrombus forming on disrupted atherothrombotic coronary plaque. Aspirin in combination with a $P2Y_{12}$ receptor blocker (e.g., clopidogrel, ticagrelor, or prasugrel) are appropriate antiplatelet options. Options for anticoagulants include (1) unfractionated heparin (UFH), long the mainstay of therapy; (2) the low-molecular-weight heparin (LMWH), enoxaparin, which has been shown to be superior to UFH in reducing recurrent cardiac events, especially in patients managed by a conservative strategy but with some increase in bleeding; (3) bivalirudin, a direct thrombin inhibitor that is similar in efficacy to either UFH or LMWH but causes less bleeding and is used just prior to and/or during percutaneous coronary intervention; and (4) the indirect factor Xa inhibitor, fondaparinux, which is equivalent in efficacy to enoxaparin but appears to have a lower risk of major bleeding. To reduce myocardial oxygen demand, beta-blockade administration targeting a heart rate of 60 beats/min is reasonable, though it should be used with caution or avoided in the presence of heart failure (not present in this patient). Likewise, nitroglycerin is a commonly used and effective anti-anginal therapy. However, a direct contraindication is the use of phosphodiesterase inhibitors (such as tadalafil in this patient), and co-administration can result in catastrophic hypotension.

IV-131. The answer is E. *(Chap. 268)* Patients with documented non–ST-elevation acute coronary syndrome (ACS) exhibit a wide spectrum of early (30 days) risk of death, ranging from 1 to 10%, and a recurrent ACS rate of 5–15% during the first year. Assessment of risk can be accomplished by clinical risk scoring systems such as that developed from the Thrombolysis in Myocardial Infarction (TIMI) Trials, which includes seven independent risk factors (age ≥65 years, 3 or more of the traditional risk factors for coronary heart disease, known history of coronary artery disease or coronary stenosis of at least 50%, daily aspirin use in the prior week, more than one anginal episode in the past 24 hours, ST-segment deviation of at least 0.5 mm, and an elevated cardiac specific biomarker above the upper limit of normal). Additional risk factors include diabetes mellitus, left ventricular dysfunction, renal dysfunction, and elevated levels of B-type natriuretic peptides.

IV-132. **The answer is B.** *(Chap. 268)* This patient has Prinzmetal variant angina. Nitrates and calcium channel blockers are the main therapeutic agents. Aspirin may actually increase the severity of ischemic episodes, possibly as a result of the sensitivity of coronary tone to modest changes in the synthesis of prostacyclin. Statin therapy has been shown to reduce the risk of major adverse events, although the precise mechanism is not established. The response to beta blockers is variable. Coronary revascularization may be helpful in patients who also have discrete, flow-limiting, proximal fixed obstructive lesions. Patients who have had ischemia-associated ventricular fibrillation despite maximal medical therapy should receive an implantable cardioverter-defibrillator.

IV-133. **The answer is A.** *(Chap. 269)* This patient is presenting with classic ischemic chest pain by history. When present in such a classic manner, it should be unmistakable. After obtaining this history, the clinical working diagnosis is acute coronary syndrome (ACS). The next most important step in the decision tree is to determine whether the patient is having an ST-elevation myocardial infarction (STEMI) or non–ST-elevation myocardial infarction, or unstable angina. This determination can only be accomplished by electrocardiogram (ECG). Serum biomarkers (troponin and CK-MB) take minutes to hours to return, and may not be elevated in the initial several hours of an infarction. In practical terms, the high-sensitivity troponin assays are of less immediate value in patients with STEMI. Contemporary urgent reperfusion strategies necessitate making a decision (based largely on a combination of clinical and ECG findings) before the results of blood tests have returned from the laboratory. While echocardiogram may demonstrate wall motion abnormalities in areas of ischemia, it cannot differentiate between ST-elevation and non–ST-elevation ACS. Coronary CT angiography is not warranted in a patient having active ischemic pain. Figure IV-133 provides a flowchart of the decision tree facing the clinician treating a patient with ischemic discomfort.



Acute coronary syndromes

	Unstable angina	NSTEMI	STEMI
Clinical history	Principle clinical presentations: 1. Rest angina or angina with minimal exertion usually lasting ≥20 mins 2. New-onset severe angina CCS grade ≥III) 3. Crescendo angina	Ischemic chest pain	Ischemic chest pain
ECG changes	Nonspecific changes	ST-segment depression or T-wave inversion	ST-segment depression
Myocardial necrosis (biomarkers, preferably cardiac troponin)	⊗	✓	✓

FIGURE IV-133 Hurst's central illustration: acute coronary syndromes. Definition of acute coronary syndromes, a term that encompasses unstable angina, non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI). Diagnosis relies on integration of information from clinical history, an initial electrocardiogram (ECG), and laboratory results. Myocardial necrosis is a necessary, but not sufficient, component of NSTEMI and STEMI. CCS, Canadian Cardiovascular Society. (Reproduced with permission from Fuster V et al: *Hurst's the Heart*, 14th ed. New York: McGraw Hill, 2017.)

IV-134. The answer is C. *(Chap. 269)* Creatine kinase rises within 4–8 hours and generally returns to normal by 48–72 hours. The cardiac troponin assays have a similar time frame for rise, but they generally last much longer, about 7–10 days after ST-elevation myocardial infarction (Figure IV-134). Early reperfusion will cause an earlier peak of biomarker measurements.

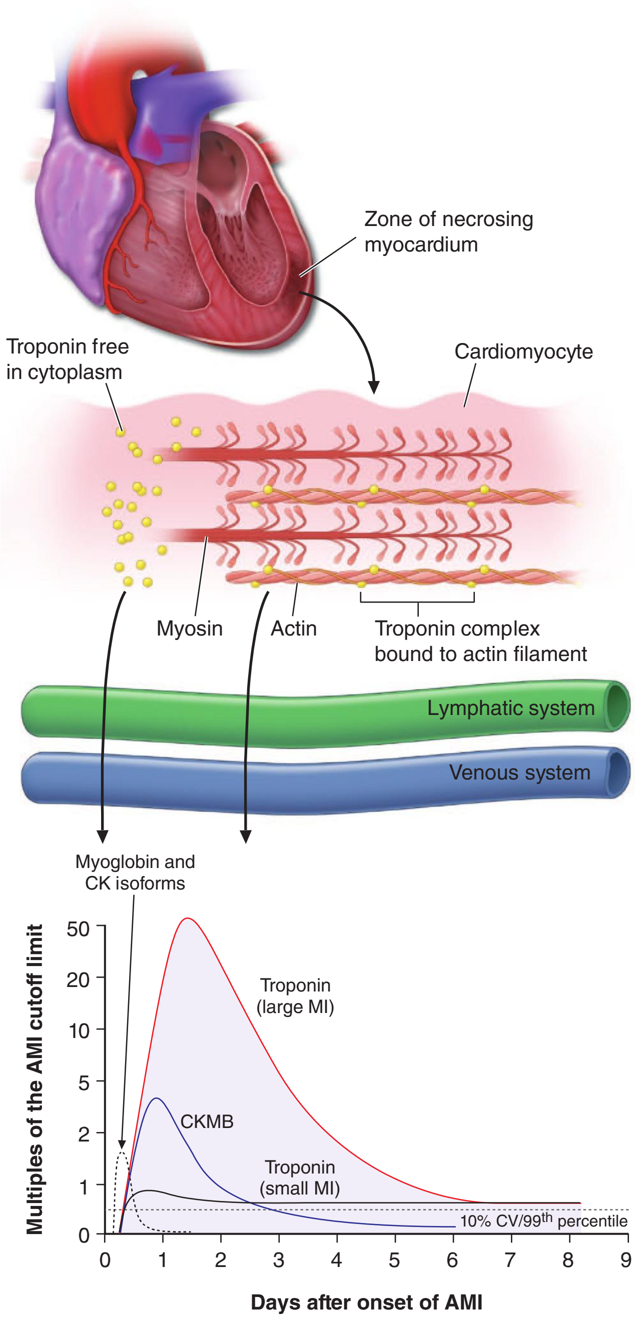

Zone of necrosing myocardium
Troponin free in cytoplasm
Cardiomyocyte
Myosin
Actin
Troponin complex bound to actin filament
Lymphatic system
Venous system
Myoglobin and CK isoforms
Multiples of the AMI cutoff limit
50
20
10
5
2
1
0
Troponin (large MI)
CKMB
Troponin (small MI)
10% CV/99th percentile
0
1
2
3
4
5
6
7
8
9
Days after onset of AMI

FIGURE IV-134 *Top:* Modified with permission from Antman EM: Decision making with cardiac troponin tests. *N Engl J Med* 346:2079, 2002. *Bottom:* Reproduced with permission from Jaffe AS et al: Biomarkers in acute cardiac disease: the present and the future. *J Am Coll Cardiol* 48:1, 2006.

IV-135. The answer is E. *(Chap. 269)* All of these choices are appropriate therapy for patients with an ST-elevation myocardial infarction (STEMI) in certain situations. Aspirin is an irreversible cyclooxygenase inhibitor and thus inhibits the production of thromboxane A_2. Beta blockers reduce myocardial oxygen demand by reducing cardiac chronotropy and inotropy. They should be used with caution in patients with MI and any signs of delayed conduction (prolonged PR interval), heart failure, or risk for cardiogenic shock. Clopidogrel inhibits the P2Y12 adenosine diphosphate platelet receptor to inhibit platelet aggregation. Abciximab and eptifibatide are glycoprotein IIb/IIIa inhibitors that also inhibit platelet aggregation. While nitroglycerin is effective for anti-anginal effects in the setting of STEMI, it enacts those effects through decreasing preload and perhaps through some direct nitric oxide–induced coronary vasodilation. Nitroglycerin has minimal effect on systemic afterload.

IV-136. The answer is E. *(Chap. 269)* This patient has an accelerated idioventricular rhythm, a common finding in patients with successful reperfusion after thrombolytic therapy. This rhythm is benign and requires no further therapy. It invariably resolves on its own. Flecainide (a class I anti-arrhythmic) is contraindicated in post–myocardial infarction patients as it was found to increase mortality in the CAST trial. Amiodarone or metoprolol would be appropriate therapy if this was ventricular tachycardia or perhaps supraventricular tachycardia. Carotid sinus massage would be appropriate in the setting of supraventricular tachycardia.

IV-137. The answer is C. *(Chap. 269)* Glucocorticoids and nonsteroidal anti-inflammatory agents, with the exception of aspirin, should be avoided in patients with ST-elevation myocardial infarction. They can impair infarct healing and increase the risk of myocardial rupture, and their use may result in a larger infarct scar. In addition, they can increase coronary vascular resistance, thereby potentially reducing flow to ischemic myocardium.

IV-138. The answer is A. *(Chap. 269)* If no contraindications are present, fibrinolytic therapy should ideally be initiated within 30 minutes of presentation (i.e., door-to-needle time ≤30 minutes). The principal goal of fibrinolysis is prompt restoration of full coronary arterial patency. The fibrinolytic agents tissue plasminogen activator (tPA), streptokinase, tenecteplase (TNK), and reteplase (rPA) have been approved by the U.S. Food and Drug Administration for IV use in patients with ST-elevation myocardial infarction. These drugs all act by promoting the conversion of plasminogen to plasmin, which subsequently lyses fibrin thrombi. Although considerable emphasis was first placed on a distinction between more fibrin-specific agents, such as tPA, and non–fibrin-specific agents, such as streptokinase, it is now recognized that these differences are only relative, as some degree of systemic fibrinolysis occurs with the former agents. TNK and rPA are referred to as bolus fibrinolytics since their administration does not require a prolonged IV infusion.

IV-139. The answer is A. *(Chap. 269)* Factors that increase the work of the heart during the initial hours of infarction may increase the size of the infarct. Therefore, patients with ST-elevation myocardial infarction should be kept at bedrest for the first 6–12 hours. However, in the absence of complications, patients should be encouraged, under supervision, to resume an upright posture by dangling their feet over the side of the bed and sitting in a chair within the first 24 hours. This practice is psychologically beneficial and usually results in a reduction in the pulmonary capillary wedge pressure. In the absence of hypotension and other complications, by the second or third day, patients typically are ambulating in their room with increasing duration and frequency, and they may shower or stand at the sink to bathe. By day 3 after infarction, patients should be increasing their ambulation progressively to a goal of 185 m (600 ft) at least three times a day.

IV-140. The answer is B. *(Chap. 269)* Clear contraindications to the use of fibrinolytic agents include a history of cerebrovascular hemorrhage at any time, a nonhemorrhagic stroke or other cerebrovascular event within the past year, marked hypertension (a reliably determined systolic arterial pressure >180 mmHg and/or a diastolic pressure >110 mmHg) at any time during the acute presentation, suspicion of aortic dissection, and active internal bleeding (excluding menses). While advanced age is associated with an increase in hemorrhagic complications, the benefit of fibrinolytic therapy in the elderly appears to justify its use if no other contraindications are present and the amount of myocardium in jeopardy appears to be substantial. Relative contraindications to fibrinolytic therapy, which require assessment of the risk-to-benefit ratio, include current use of anticoagulants (international normalized ratio ≥2), a recent (<2 weeks) invasive or surgical procedure or prolonged (>10 minutes) cardiopulmonary resuscitation, known bleeding diathesis, pregnancy, a hemorrhagic ophthalmic condition (e.g., hemorrhagic diabetic retinopathy), active peptic ulcer disease, and a history of severe hypertension that is currently adequately controlled. Because of the risk of an allergic reaction, patients should not receive streptokinase if that agent had been received within the preceding 5 days to 2 years.

IV-141. The answer is D. *(Chap. 270)* Percutaneous therapy of coronary artery disease underwent a paradigm shift with the introduction of coronary stents in 1994. However, metallic stents are also prone to stent thrombosis (1–3%), either acute (<24 hours) or subacute (1–30 days), which can be ameliorated by greater attention to full initial stent deployment and the use of dual antiplatelet therapy (DAPT) (aspirin, plus a platelet P2Y12 receptor blocker [clopidogrel, prasugrel, or ticagrelor]). Late (30 days to 1 year) and very late stent thrombosis (>1 year) occur very infrequently with stents but are slightly more common with first-generation drug-eluting stents, necessitating DAPT for up to 1 year or longer. Use of the second-generation stents (such as Mrs. Heyward's everolimus-eluting stent) is associated with lower rates of late and very late stent thrombosis, and shorter durations of DAPT may be possible. Premature discontinuation of DAPT, particularly in the first month after implantation, is associated with a significantly increased risk for stent thrombosis (3–9× greater). Stent thrombosis results in death in 10–20% and myocardial infarction in 30–70% of patients. Elective surgery (such as Mrs. Heyward's cataract removal) that requires discontinuation of antiplatelet therapy after drug-eluting stent implantation should be postponed until after 6 months and preferably after 1 year, if at all possible. At that point, clopidogrel can be reasonably discontinued if no other mitigating factors are present. If at all possible, aspirin should be continued.

IV-142. The answer is E. *(Chap. 270)* Serious complications during percutaneous coronary intervention are rare but include a mortality rate of 0.1–0.3% for elective cases, a large myocardial infarction in <3%, and stroke in <0.1%. Patients who are elderly (>65 years), undergoing an emergent or urgent procedure, have chronic kidney disease, present with an ST-segment elevation myocardial infarction, or are in shock have significantly higher risk.

IV-143. and 144. The answers are C and D, respectively. *(Chap. 271)* This patient presents at a young age with hypertension that is difficult to control, raising the question of secondary causes of hypertension. The most likely diagnosis in this patient is primary hyperaldosteronism, also known as Conn syndrome. The patient has no physical features that suggest congenital adrenal hyperplasia or Cushing syndrome. In addition, there is no glucose intolerance as is commonly seen in Cushing syndrome. The lack of episodic symptoms and the labile hypertension make pheochromocytoma unlikely. The findings of hypokalemia and metabolic alkalosis in the presence of difficult-to-control hypertension yield the likely diagnosis of Conn syndrome. Diagnosis of the disease can be difficult, but the preferred test is the plasma aldosterone/renin ratio. This test should be performed at 8 a.m., and a ratio greater than 30–50 is diagnostic of primary hyperaldosteronism. Caution should be made in interpreting this test while the patient is on angiotensin-converting enzyme (ACE) inhibitor therapy as ACE inhibitors can falsely elevate plasma renin activity. However, a plasma renin level that is undetectable or an elevated aldosterone/renin ratio in the presence of an ACE inhibitor therapy is highly suggestive of primary hyperaldosteronism. Selective adrenal vein renin sampling may be performed after the diagnosis to help determine whether the process is unilateral or bilateral. Although fibromuscular dysplasia is a common secondary cause of hypertension in young females, the presence of hypokalemia and metabolic alkalosis should suggest Conn syndrome. Thus, MRI of the renal arteries is unnecessary in this case. Measurement of 24-hour urine collection for potassium wasting and aldosterone secretion can be useful in the diagnosis of Conn syndrome. The measurement of metanephrines or cortisol is not indicated.

IV-145. The answer is C. *(Chap. 271)* This patient is suffering from a hypertensive emergency, specifically malignant hypertension. Hallmarked by rapid arterial changes and loss of cerebral autoregulation, the clinical signs include very high blood pressure, delirium due to cerebral hyperperfusion, renal failure with proteinuria and hematuria, and hemolytic anemia. Mortality in the first several hours is high with this disease state, and rapid treatment is warranted. However, most patients presenting with malignant hypertension also have long-standing chronic elevations in blood pressure, and a change in the "set point" of the cerebral autoregulation. Reducing the blood pressure rapidly to normal levels for the regular population often leads to hypoperfusion and can lead to watershed cerebral infarcts. In the setting of a hypertensive emergency, a reduction of mean arterial pressure in minutes to hours by 25% is recommended. Parenteral therapy is more rapid onset and much more easily titrated than oral therapy, which is inappropriate in the emergent setting. Immediate-release nifedipine is particularly potent and is associated with a higher risk of myocardial infarction when used in this setting. Plasmapheresis would be warranted if this were a case of thrombotic thrombocytopenic purpura (TTP), but with the normal platelet count in this case it is unlikely TTP.

IV-146. The answer is E. *(Chap. 271)* In the United States, ~78 million adults have hypertension. Hypertension prevalence is 33.5% in non-Hispanic blacks, 28.9% in non-Hispanic whites, and 20.7% in Mexican Americans. In African Americans, hypertension appears earlier, is generally more severe, and results in higher rates of morbidity and mortality from stroke, left ventricular hypertrophy, congestive heart failure, and end-stage renal disease than in white Americans. According to the National Health and Nutrition Examination Survey data, in 2007–2010, 81.5% of those with hypertension were aware they had it, 74.9% were being treated, but only 52.5% were controlled.

IV-147. The answer is D. *(Chap. 271)* To provide a framework for understanding the pathogenesis and treatment options for hypertensive disorders, it is useful to understand factors involved in the regulation of both normal and elevated arterial pressure (Figure IV-147). Cardiac output and peripheral resistance are the two determinants of arterial pressure. Cardiac output is determined by stroke volume and heart rate; stroke volume is related to myocardial contractility and to the size of the vascular compartment. Peripheral resistance is determined by functional and anatomic changes in small arteries (lumen diameter 100–400 μm) and arterioles.

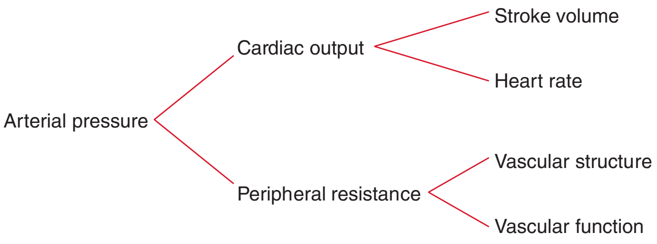


FIGURE IV-147

IV-148. The answer is A. *(Chap. 271)* Inherited pheochromocytomas may be associated with multiple endocrine neoplasia type 2A and type 2B, von Hippel-Lindau disease, and neurofibromatosis. Liddle syndrome is due to mutations in subunits of the epithelial sodium channel *SCNN1B* and *SCNN1C* genes and causes hypertension and hypokalemia in the setting of low renin and low potassium.

IV-149. The answer is B. *(Chap. 272)* Renal artery stenosis (RAS) is common and often has only minor hemodynamic effects. The earliest finding may be an elevated systemic renin level. Fibromuscular dysplasia (FMD) is reported in 3–5% of normal subjects presenting as potential kidney donors without hypertension. It may present clinically with hypertension in younger individuals (between age 15 and 50), most often women. FMD does not often threaten kidney function, but it sometimes produces total occlusion and can be associated with renal artery aneurysms. Critical levels of stenosis lead to a reduction in perfusion pressure that activates the renin-angiotensin system, reduces sodium excretion, and activates sympathetic adrenergic pathways. These events lead to systemic hypertension characterized by angiotensin dependence in the early stages; widely varying pressures; loss of circadian blood pressure rhythms; and accelerated target organ injury, including left ventricular hypertrophy and renal fibrosis. Renovascular hypertension can be treated with agents that block the renin-angiotensin system and other drugs that modify these pressor pathways. Elevated renal artery velocities by Doppler ultrasound greater than 200 cm/s generally predict hemodynamically important lesions (greater than 60% vessel lumen occlusion). While renin levels and activity are elevated in the state of significant RAS, the relative level does not predict response to therapy.

IV-150. The answer is B. *(Chap. 272)* This patient's clinical scenario is most consistent with atheroembolic renal disease. Atheroemboli in the kidney are strongly associated with aortic aneurysmal disease and renal artery stenosis. Most clinical cases can be linked to precipitating events, such as angiography, vascular surgery, anticoagulation with heparin, thrombolytic therapy, or trauma. Clinical manifestations of this syndrome commonly develop between 1 and 14 days after an inciting event and may continue to develop for weeks thereafter. Systemic embolic disease manifestations, such as fever, abdominal pain, and weight loss, are present in less than half of patients, although cutaneous manifestations including livedo reticularis and localized toe gangrene may be more common. Worsening hypertension and deteriorating kidney function are common. Typical laboratory findings include rising creatinine, transient eosinophilia (60–80% of cases), elevated sedimentation rate, and hypocomplementemia (15% of cases). Contrast-induced nephropathy is not associated with fever, high erythrocyte sedimentation rate, eosinophilia, or livedo reticularis of the lower extremities. It would be unusual to develop interstitial nephritis without exposure to a new medication, and other than eosinophilia the laboratory abnormalities are not supportive in this case. Likewise, the sudden development of hypereosinophilic syndrome in a 75-year-old man would be highly unlikely. Finally, while Churg-Strauss syndrome is a small-to-medium vessel vasculitis associated with renal dysfunction and eosinophilia, almost all patients experience atopy and asthma-like lung disease, which are absent in this patient.

IV-151. The answer is C. *(Chap. 272)* The CT angiogram shows loss of circulation to the upper pole of the right kidney. In a patient with atrial fibrillation and noncompliance with anticoagulation, the concern is thromboembolism, which explains the presentation. Clinical manifestations vary depending on the rapidity of onset and extent of occlusion. Acute arterial thrombosis may produce flank pain, fever, leukocytosis, nausea, and vomiting. If kidney infarction results, enzymes such as lactate dehydrogenase rise to extreme levels. If both kidneys are affected, renal function will decline precipitously with a drop in urine output. If a single kidney is involved, renal functional changes may be minor. Hypertension related to sudden release of renin from ischemic tissue can develop rapidly, as long as some viable tissue in the "peri-infarct" border zone remains. If the infarct zone demarcates precisely, the rise in blood pressure and renin activity may resolve. Diagnosis of renal infarction may be established by vascular imaging with MRI, CT angiography, or arteriography

IV-152. The answer is B. *(Chap. 273)* The D-dimer measured by enzyme-linked immunosorbent assay (ELISA) is elevated in the setting of breakdown of fibrin by plasmin, and the presence of a positive D-dimer can prompt the need for additional imaging for deep venous thrombosis and/or pulmonary embolus in specific clinical situations where the patient would be considered to have an elevation in D-dimer. However, one must be cautious about placing value on an elevated D-dimer in other situations where there can be an alternative explanation for the elevated level. Of the scenarios listed in the question, the only patient who would be expected to have a negative D-dimer would be the patient with calf pain and recent air travel. The presence of a normal alveolar-arterial oxygen gradient cannot reliably differentiate between those with and without pulmonary embolism. In all the other scenarios, elevations in D-dimer could be related to other medical conditions and provide no diagnostic information to inform the clinician regarding the need for further evaluation. Some common clinical situations in which the D-dimer is elevated include sepsis, myocardial infarction, cancer, pneumonia, the postoperative state, and the second and third trimesters of pregnancy.

IV-153. The answer is C. *(Chap. 273)* Many patients with pulmonary embolism (PE) have no evidence of deep venous thrombosis because the clot has already embolized to the lungs. The most common gas exchange abnormalities are arterial hypoxemia and an increased alveolar-arterial O_2 tension gradient, which represents the inefficiency of O_2 transfer across the lungs. Physiologic dead space increases because ventilation to gas exchange units exceeds blood flow through the pulmonary capillaries. Other pathophysiologic abnormalities include (1) increased pulmonary vascular resistance due to vascular obstruction or platelet secretion of vasoconstricting neurohumoral agents, such as serotonin (release of vasoactive mediators can produce ventilation-perfusion mismatching at sites remote from the embolus, thereby accounting for discordance between a small PE and a large alveolar-arterial O_2 gradient); (2) impaired gas exchange due to increased alveolar dead space from vascular obstruction, hypoxemia from ventilation-perfusion mismatching, right-to-left shunting, or impaired carbon monoxide diffusion capacity due to loss of gas exchange surface; (3) alveolar hyperventilation due to reflex stimulation of irritant receptors; (4) increased airway resistance due to mediator-induced bronchoconstriction; and (5) decreased pulmonary compliance due to lung edema, lung hemorrhage, or loss of surfactant. In the setting of acute PE, pulmonary vascular resistance and thus right ventricular (RV) pressures acutely rise. Hypotension in this setting is due to acute RV failure. The left ventricle is often contracting in a hyperdynamic fashion due to a catecholamine surge and compression from the dilated, failing RV.

IV-154. The answer is C. *(Chap. 273)* This patient is suffering from massive pulmonary embolism (PE) as a complication of her bariatric surgery. Rather than being defined by the absolute size of clot burden of PE on imaging, massive PE is defined by the presence of hypotension due to the embolism. Usually, one would consider emergent thrombolysis (either systemic or catheter directed) for a patient with massive PE, but this patient has recently completed a large open abdominal operation, which is a direct contraindication for thrombolytics, such as tissue plasminogen activator or urokinase, as she would be at very high risk for life-threatening hemorrhage. In this case, the goal is to alleviate right heart obstruction as soon and as effectively as possible. Emergent surgical pulmonary embolectomy provides this, and it should be pursued before the onset of multisystem organ failure renders the surgery too high risk. Inferior vena cava (IVC) filter placement could be pursued later if it is discovered that the patient has residual lower extremity thrombus. While systemic anticoagulation will be needed after embolectomy, enoxaparin represents a poor choice given the patients very high body weight and the only partially reversible nature of the low-molecular-weight heparin, a consideration given the patient's high risk of bleeding.

IV-155. The answer is E. *(Chap. 273)* Massive pulmonary embolism (PE) accounts for 5–10% of cases, and it is characterized by extensive thrombosis affecting at least half of the pulmonary vasculature. Dyspnea, syncope, hypotension, and cyanosis are hallmarks of massive PE. Patients with massive PE may present in cardiogenic shock and can die from multisystem organ failure. Submassive PE accounts for 20–25% of patients, and it is characterized by right ventricular dysfunction despite normal systemic arterial pressure. The combination of right heart failure and release of cardiac biomarkers indicates a high risk of clinical deterioration and Mr. Casey fits this profile. Low-risk PE constitutes about 65–75% of cases. These patients have an excellent prognosis. Saddle PE is an anatomic term and refers to a clot straddling the pulmonary artery bifurcation.

IV-156. The answer is E. *(Chap. 273)* Prevention of deep venous thrombosis and pulmonary embolism is of paramount importance because venous thromboembolism (VTE) is difficult to detect and poses a profound medical and economic burden. Low-dose unfractionated heparin or low-molecular-weight heparin is the most common form of in-hospital prophylaxis (Table IV-156). Computerized reminder systems can increase the use of preventive measures and, at Brigham and Women's Hospital, they have reduced the symptomatic VTE rate by >40%. Audits of hospitals to ensure that prophylaxis protocols are

TABLE IV-156 Prevention of Venous Thromboembolism Among Hospitalized Patients

Condition	Prophylaxis Strategy
High-risk nonorthopedic surgery	Unfractionated heparin 5000 units SC bid or tid Enoxaparin 40 mg daily Dalteparin 2500 or 5000 units daily
Cancer surgery, including gynecologic cancer surgery	Enoxaparin 40 mg daily, consider 1 month of prophylaxis
Major orthopedic surgery	Warfarin (target INR 2.0–3.0) Enoxaparin 40 mg daily Enoxaparin 30 mg bid Dalteparin 2500 or 5000 units daily Fondaparinux 2.5 mg daily Rivaroxaban 10 mg daily, beginning 6–10 h postoperatively Aspirin 81–325 mg daily Dabigatran 110 mg first day, then 220 mg daily Apixaban 2.5 mg bid, beginning 12–24 h postoperatively Intermittent pneumatic compression (with or without pharmacologic prophylaxis)
Medically ill patients, during hospitalization	Unfractionated heparin 5000 units bid or tid Enoxaparin 40 mg daily Dalteparin 2500 or 5000 units daily Fondaparinux 2.5 mg daily
Medically ill patients, during and after hospitalization	Betrixaban 80 mg daily for 35–42 days
Anticoagulation contraindicated	Intermittent pneumatic compression devices (but whether graduated compression stockings are effective in medical patients remains uncertain)

Abbreviation: INR, international normalized ratio; SC, subcutaneously.

being used will also increase utilization of preventive measures. Duration of prophylaxis is an important consideration. Patients with a contraindication to anticoagulation should receive sequential compression devices.

IV-157. The answer is C. *(Chap. 274)* An aneurysm is defined as a pathologic dilation of a segment of a blood vessel. A true aneurysm involves all three layers of the vessel wall and is distinguished from a pseudo-aneurysm, in which the intimal and medial layers are disrupted and the dilated segment of the aorta is lined by adventitia only and, at times, by perivascular clot.

IV-158. The answer is D. *(Chap. 274)* Familial clusterings of aortic aneurysms occur in 20% of patients, suggesting a hereditary basis for the disease. Mutations of the gene that encodes fibrillin-1 are present in patients with Marfan syndrome. Fibrillin-1 is an important component of extracellular microfibrils, which support the architecture of elastic fibers and other connective tissue. Deficiency of fibrillin-1 in the extracellular matrix leads to excessive signaling by transforming growth factor-β (TGF-β). Loeys-Dietz syndrome is caused by mutations in the genes that encode TGF-β receptor 1 (TGFBR1) and 2 (TGFBR2). Increased signaling by TGF-β and mutations of TGFBR1, TGFBR2, TGFBR3, and TGFB2 and TGFB3, may cause thoracic aortic aneurysms. Mutations of SMAD3, which encodes a downstream signaling protein involved with TGF binding to its receptors, have been described in a syndrome of thoracic aortic aneurysm; craniofacial, skeletal, and cutaneous anomalies; and osteoarthritis. Mutations of the genes encoding the smooth muscle–specific alpha-actin (ACTA2), smooth muscle cell–specific myosin heavy chain 11 (MHC11), and myosin light chain kinase (MYLK) and mutations of TGFBR2 and SMAD3 have been reported in some patients with nonsyndromic familial thoracic aortic aneurysms. Mutations of the *STK11* gene cause most cases of Peutz-Jeghers syndrome. Mutations of type III procollagen have been implicated in Ehlers-Danlos type IV syndrome. The *CFTR* gene mutation is responsible for cystic fibrosis.

IV-159. **The answer is E.** *(Chap. 274)* Spondyloarthropathies such as ankylosing spondylitis, rheumatoid arthritis, psoriatic arthritis, relapsing polychondritis, and reactive arthritis (formerly known as Reiter syndrome) are associated with dilation of the ascending aorta. Aortic aneurysms occur in patients with Behçet syndrome, Cogan syndrome, and IgG4-related systemic disease.

IV-160. **The answer is D.** *(Chap. 274)* The risk of aortic aneurysm rupture is most substantially related to the size of the aneurysm and the presence of symptoms, ranging approximately from 2–3% per year for thoracic aortic aneurysms <4.0 cm in diameter to 7% per year for those >6 cm in diameter.

IV-161. **The answer is E.** *(Chap. 274)* Bicuspid aortic valve is commonly associated with thoracic, ascending aortic aneurysms. Replacement of the ascending aorta >4.5 cm is reasonable in patients with bicuspid aortic valves undergoing aortic valve replacement because of severe aortic stenosis or aortic regurgitation.

IV-162. **The answer is E.** *(Chap. 275)* Mr. Tomazelli is describing classic symptoms of claudication due to peripheral arterial disease (PAD). By far, the most common etiology of this disease is atherosclerosis, particularly in elderly patients with hypertension, diabetes mellitus, and a smoking history. The history and physical examination are often sufficient to establish the diagnosis of PAD. An objective assessment of the presence and severity of disease is obtained by noninvasive techniques. MR angiography, invasive catheter-based angiography, or CT angiography are not initial tests of choice but may be used to plan revascularization strategies. The initial test of choice is an ankle-brachial index (ABI). Arterial pressure can be recorded noninvasively in the legs by placement of sphygmomanometer cuffs at the ankles and the use of a Doppler device to auscultate or record blood flow from the dorsalis pedis and posterior tibial arteries. Normally, systolic blood pressure in the legs and arms is similar. Indeed, ankle pressure may be slightly higher than arm pressure due to pulse-wave amplification. Thus, the ratio of the ankle and brachial artery pressures (termed the ankle:brachial index [ABI]) is 1.00–1.40 in normal individuals. In the presence of hemodynamically significant lower extremity stenoses, the systolic blood pressure in the leg is decreased. ABI values of 0.91–0.99 are considered “borderline,” and those <0.90 are abnormal and diagnostic of PAD. One may also consider the pulse volume contour, which is blunted in cases of PAD.

IV-163. **The answer is D.** *(Chap. 275)* This patient has a classic presentation of thromboangiitis obliterans, or Buerger disease. This is an inflammatory occlusive vascular disorder involving small- and medium-sized arteries and veins in the distal upper and lower extremities. Cerebral, visceral, and coronary vessels may be affected rarely. This disorder develops most frequently in men <40 years of age who are smokers. The prevalence is higher in Asians and individuals of Eastern European descent. Although the cause of thromboangiitis obliterans is not known, there is a definite relationship to cigarette smoking in patients with this disorder. The clinical features of thromboangiitis obliterans often include a triad of claudication of the affected extremity, Raynaud phenomenon (per the picture), and migratory superficial vein thrombophlebitis. Claudication usually is confined to the calves and feet or the forearms and hands because this disorder primarily affects distal vessels. There is no specific treatment except abstention from tobacco. The prognosis is worse in individuals who continue to smoke, but results are discouraging even in those who stop smoking. Arterial bypass of the larger vessels may be used in selected instances, as well as local debridement, depending on the symptoms and severity of ischemia. Antibiotics may be useful when infection is present. Anticoagulants and glucocorticoids are not helpful. Cilostazol is a phosphodiesterase inhibitor used for intermittent claudication but has no proven role in thromboangiitis obliterans. In some cases of advanced disease, amputation may be required.

IV-164. **The answer is E.** *(Chap. 275)* Thoracic outlet compression syndrome is a symptom complex resulting from compression of the neurovascular bundle (artery, vein, or nerves) at the thoracic outlet as it courses through the neck and shoulder. Cervical ribs, abnormalities of the scalenus anticus muscle, proximity of the clavicle to the first rib, or abnormal insertion of the pectoralis minor muscle may compress the subclavian artery, subclavian vein, and brachial plexus as these structures pass from the thorax to the arm. Depending on the structures affected, thoracic outlet compression syndrome is divided into arterial, venous, and neurogenic forms. Patients with neurogenic thoracic outlet compression may develop shoulder and arm pain, weakness, and paresthesias. Patients with arterial compression may experience claudication, Raynaud phenomenon, and even ischemic tissue loss and gangrene. Venous compression may cause thrombosis of the subclavian and axillary veins; this is often associated with effort and is referred to as Paget-Schroetter syndrome. Several maneuvers that support the diagnosis of arterial thoracic outlet compression syndrome may be used to precipitate symptoms, cause a subclavian artery bruit, and diminish arm pulses. These maneuvers include the abduction and external rotation test, in which the affected arm is abducted by 90° and the shoulder is externally rotated; the scalene maneuver (extension of the neck and rotation of the head to the side of the symptoms); the costoclavicular maneuver (posterior rotation of shoulders); and the hyperabduction maneuver (raising the arm 180°). Most patients can be managed conservatively. They should be advised to avoid the positions that cause symptoms. Many patients benefit from shoulder girdle exercises. Surgical procedures such as removal of the first rib and resection of the scalenus anticus muscle are necessary occasionally for relief of symptoms, particularly in athletes, or treatment of ischemia.

IV-165. **The answer is E.** *(Chap. 275)* This patient has an acquired arteriovenous fistula with resultant high-output heart failure. Acquired arteriovenous fistulas either are created to provide vascular access for hemodialysis or occur as a result of a penetrating injury such as a gunshot or knife wound or as complications of arterial catheterization or surgical dissection. The clinical features depend on the location and size of the fistula. Frequently, a pulsatile mass is palpable, and a thrill and a bruit lasting throughout systole and diastole are present over the fistula. With long-standing fistulas, clinical manifestations of chronic venous insufficiency, including peripheral edema; large, tortuous varicose veins; and stasis pigmentation become apparent because of the high venous pressure. Evidence of ischemia may occur in the distal portion of the extremity. Skin temperature is higher over the arteriovenous fistula. Large arteriovenous fistulas may result in an increased cardiac output with consequent cardiomegaly and high-output heart failure. The diagnosis is often evident from the physical examination. Compression of a large arteriovenous fistula may cause reflex slowing of the heart rate (Nicoladoni-Branham sign). Acquired arteriovenous fistulas are usually amenable to surgical treatment that involves division or excision of the fistula. Occasionally, autogenous or synthetic grafting is necessary to reestablish continuity of the artery and vein.

IV-166. **The answer is B.** *(Chap. 276)* Varicose veins are dilated, bulging, tortuous superficial veins, measuring at least 3 mm in diameter. The estimated prevalence of varicose veins in the United States is approximately 15% in men and 30% in women. Chronic venous insufficiency is a consequence of incompetent veins in which there is venous hypertension and extravasation of fluid and blood elements into the tissue of the limb. It may occur in patients with varicose veins but usually is caused by disease in the deep veins. Chronic venous insufficiency with edema affects approximately 7.5% of men and 5% of women, and the prevalence increases with age ranging from 2% among those less than 50 years of age to 10% of those 70 years of age. Approximately 20% of patients with chronic venous insufficiency develop venous ulcers.

IV-167. **The answer is B.** *(Chap. 276)* Diuretics are contraindicated in patients with lymphedema and may cause depletion of intravascular volume and metabolic abnormalities. Patients should be encouraged to participate in physical activity; frequent leg elevation can reduce the amount of edema. Psychosocial support is indicated to assist patients cope with anxiety or depression related to body image, self-esteem, functional disability, and fear of limb loss. Physical therapy, including massage to facilitate lymphatic drainage, may be helpful. The type of massage used in decongestive physiotherapy for lymphedema involves mild compression of the skin of the affected extremity to dilate the lymphatic channels and enhance lymphatic motility. Multilayered, compressive bandages are applied after each massage session to reduce recurrent edema. After optimal reduction in limb volume by decongestive physiotherapy, patients can be fitted with graduated compression hose. Occasionally, intermittent pneumatic compression devices can be applied at home to facilitate reduction of the edema. Liposuction in conjunction with decongestive physiotherapy may be considered to treat lymphedema, particularly postmastectomy lymphedema. Other surgical interventions are rarely used and often not successful in ameliorating lymphedema. Microsurgical lymphatico-venous anastomotic procedures have been performed to rechannel lymph flow from obstructed lymphatic vessels into the venous system. Limb reduction procedures to resect subcutaneous tissue and excessive skin are performed occasionally in severe cases of lymphedema to improve mobility.

IV-168. The answer is A. *(Chap. 276)* Varicose veins usually are treated with conservative measures. Symptoms often decrease when the legs are elevated periodically, prolonged standing is avoided, and elastic support hose are worn. External compression with elastic stockings or stretch bandages provides a counterbalance to the hydrostatic pressure in the veins. Although compression garments may improve symptoms, they do not prevent progression of varicose veins. Graduated compression stockings with pressures of 20–30 mmHg are suitable for most patients with simple varicose veins, although pressures of 30–40 mmHg may be required for patients with manifestations of venous insufficiency such as edema and ulcers.

IV-169. The answer is D. *(Chap. 277)* While each of the tests can be part of the systematic investigation of a patient with suspected or confirmed pulmonary hypertension, right heart catheterization with pulmonary vasodilator testing remains the gold standard both to establish the diagnosis of pulmonary hypertension and to guide selection of appropriate medical therapy. Ventilation/perfusion testing still has a role in screening for the presence of chronic thromboembolic pulmonary hypertension.

IV-170. The answer is D. *(Chap. 277)* This patient has a positive pulmonary vasodilator response. A decrease in mean pulmonary arterial pressure (mPAP) by ≥10 mmHg to an absolute level ≤40 mmHg without a decrease in cardiac output is defined as a positive pulmonary vasodilator response, and responders are considered for long-term treatment with calcium channel blockers (CCBs). Less than 15% of patients are deemed vasoreactive during testing, and even fewer exhibit long-term responsiveness to CCB. Nevertheless, in this patient initial therapy should include a CCB. An acute vasodilator-induced reduction in pulmonary vascular resistance and mPAP predict better long-term survival even among those patients not treated with CCB.

IV-171. The answer is C. *(Chap. 277)* Normal pulmonary function tests and CT scan make chronic lung disease unlikely. The elevated pulmonary capillary wedge pressure rules out idiopathic pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension, as it is normal in those disorders. The identical wedge pressure and left ventricular end-diastolic pressure render mitral stenosis unlikely, because with significant mitral stenosis there should be a gradient between the pulmonary capillary wedge pressure and end-diastolic left ventricle pressure. These results are consistent with post-capillary pulmonary hypertension (or pulmonary venous hypertension) due to left heart disease. Whatever the cause of elevated left atrial pressure (i.e., systolic or diastolic heart failure or valvular disease), the increased pulmonary venous pressure indirectly leads to a rise in pulmonary arterial pressure. The catheterization results combined with the normal left ventricular ejection fraction on echocardiogram make heart failure with preserved ejection fraction the most likely etiology of his pulmonary hypertension. The presence of pulmonary hypertension portends a poor prognosis in all forms of heart failure.

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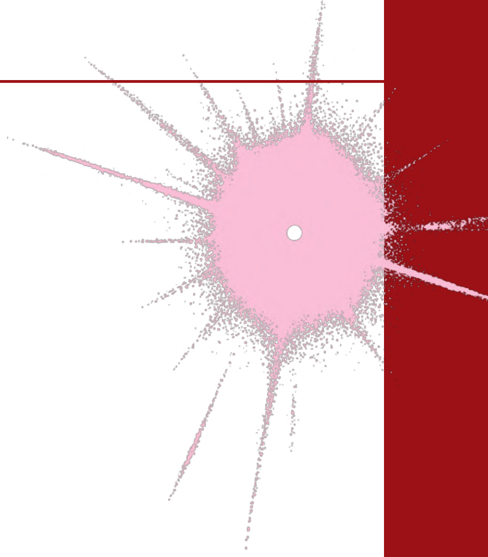
SECTION V

Disorders of the Respiratory System and Critical Care Illness



QUESTIONS

DIRECTIONS: Choose the one best response to each question.

V-1. A 25-year-old man is brought to the emergency department by ambulance after his family found him unresponsive at home. He has a history of IV drug abuse and HIV with medical noncompliance. His last CD4 count was <200/μL. On initial evaluation, his blood pressure is 120/75, heart rate is 105 beats/min, respiratory rate is 8 breaths/min, SaO_2 is 83%, and temperature is 36.0°C (96.8°F). A blood gas on room air reveals pH of 7.16, PCO_2 of 70 mmHg, and PO_2 of 55 mmHg. Which of the following is the most likely diagnosis?

A. Asthma
B. Narcotic overdose
C. Pneumococcal pneumonia
D. Pneumocystis pneumonia
E. Pulmonary embolism

V-2. A 78-year-old female is evaluated by her primary care physician for worsening dyspnea on exertion. She has a history of rheumatoid arthritis (RA) treated with anti-tumor necrosis factor alpha therapy, which has controlled her joint manifestations. She had previously been on chronic prednisone for many years and has suffered several vertebral compression fractures with resulting kyphoscoliosis. On pulmonary function testing, she has an FEV_1/FVC ratio of 82%, with an FVC of 58% predicted. Which of the following additional findings suggest that her dyspnea may be related to RA-associated interstitial lung disease?

A. A total lung capacity of 55% predicted with a diffusing capacity for carbon dioxide (DLCO) of 50% predicted
B. A total lung capacity of 55% predicted and a DLCO of 90% predicted
C. A total lung capacity of 90% predicted with a normal DLCO
D. A total lung capacity of 120% predicted with a DLCO of 60% predicted
E. A total lung capacity of 120% predicted with a DLCO of 110%

V-3. A 65-year-old man is evaluated for progressive dyspnea on exertion that has occurred over the course of the last 3 months. His medical history is significant for an episode of necrotizing pancreatitis that resulted in multiorgan failure and acute respiratory distress syndrome. He required mechanical ventilation for 6 weeks prior to his recovery. He also has a history of 30 pack-years of tobacco, quitting 15 years previously. He is not known to have chronic obstructive pulmonary disease. On physical examination, a low-pitched inspiratory and expiratory wheeze is heard, loudest over the mid-chest area. On pulmonary function testing, the FEV_1 is 2.5 L (78% predicted), FVC is 4.00 L (94% predicted), and the FEV_1/FVC ratio is 62.5%. The flow-volume curve is shown in Figure V-3A. What is the most likely cause of the patient's symptoms?

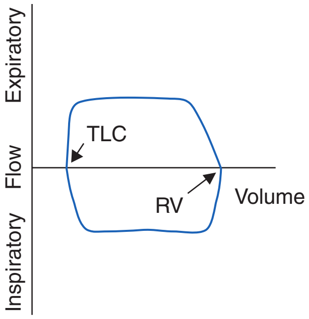


FIGURE V-3A *Abbreviations:* RV, residual volume; TLC, total lung capacity.

A. Aspirated foreign body
B. Chronic obstructive pulmonary disease
C. Idiopathic pulmonary fibrosis
D. Subglottic stenosis
E. Unilateral vocal cord paralysis

V-4 to V-7. Match each of the following pulmonary function test results to the respiratory disorder in which it is most likely to be found.

V-4. Myasthenia gravis

V-5. Idiopathic pulmonary fibrosis

V-6. Familial pulmonary hypertension

V-7. Chronic obstructive pulmonary disease

A. Increased total lung capacity (TLC), decreased vital capacity (VC), decreased FEV_1/FVC ratio
B. Decreased TLC, decreased VC, decreased residual volume (RV), increased FEV_1/FVC ratio, normal maximum inspiratory pressure (MIP)
C. Decreased TLC, increased RV, normal FEV_1/FVC ratio, decreased MIP
D. Normal TLC, normal RV, normal FEV_1/FVC ratio, normal MIP

V-8. A 78-year-old woman is admitted to the medical intensive care unit (ICU) with multilobar pneumonia. On initial presentation to the emergency department, her initial oxygen saturation was 60% on room air and only increased to 82% on a nonrebreather face mask. She was in marked respiratory distress and intubated in the emergency department. On admission to the ICU, she was sedated and paralyzed. The ventilator is set in the assist control mode with a respiratory rate of 24 breaths/min, tidal volume of 6 mL/kg, FiO_2 of 1.0, and positive end-expiratory pressure of 12 cmH_2O. An arterial blood gas measurement is performed on these settings; the results are pH of 7.20, $PaCO_2$ of 32 mmHg, and PaO_2 of 54 mmHg. What is the cause of the hypoxemia?

A. Hypoventilation alone
B. Hypoventilation and ventilation-perfusion mismatch
C. Shunt
D. Ventilation-perfusion mismatch

V-9. Which of the following disorders will cause an increase in functional residual capacity?

A. Emphysema
B. Myasthenia gravis (diaphragmatic weakness)
C. Obesity
D. Pulmonary fibrosis
E. Thoracic spinal cord transection (abdominal muscle paralysis)

V-10. Ms. Puhl, a 32-year-old woman with a long-standing history of asthma, comes to the emergency department complaining of shortness of breath typical of her asthma exacerbations after visiting a friend's who had seven cats in the house. On examination, she has diffuse bilateral polyphonic wheezes and is using accessory muscles to breathe. Her initial arterial blood gas on room air shows a pH of 7.34, $PaCO_2$ of 32 mmHg, and PaO_2 of 48 mmHg. After placing her on 40% oxygen by face mask, a repeat PaO_2 is 200 mmHg and $PaCO_2$ is 32 mmHg. The most likely cause of her initial hypoxemia was:

A. Alveolar hypoventilation
B. Diffusion defect
C. Increased dead space
D. Shunt
E. Ventilation-perfusion mismatch

V-11. A 65-year-old man is evaluated for progressive dyspnea on exertion and dry cough that have worsened over the course of 6 months. He has not had dyspnea at rest and denies recent wheezing or chest pain. He has a history of coronary artery disease and atrial fibrillation and previously underwent coronary artery bypass surgery 12 years previously. His medications include metoprolol, aspirin, warfarin, and enalapril. He previously smoked 1 pack of cigarettes daily for 40 years, quitting 5 years previously. His vital signs are as follows: blood pressure 122/68, heart rate 68 beats/min, respiratory rate 18 breaths/min, and oxygen saturation 92% on room air. His chest examination demonstrates bibasilar crackles present about one-third of the way up bilaterally. No wheezing is heard. He has an irregularly irregular rhythm with a II/VI holosystolic murmur at the apex. The jugular venous pressure is not elevated. No edema is present, but clubbing is noted. Pulmonary function testing reveals an FEV_1 of 65%, FVC of 67% predicted, FEV_1/FVC ratio of 74%, total lung capacity of 68% predicted, and diffusion capacity for carbon monoxide of 62% predicted. Which test is most likely to determine the etiology of the patient's dyspnea?

A. Bronchoscopy with transbronchial lung biopsy
B. Echocardiography
C. High-resolution CT scan of the chest
D. Nuclear medicine cardiac stress test
E. Positron emission tomography scan

V-12. A 34-year-old African American female is evaluated for progressive dyspnea on exertion and nonproductive cough. She has previously been diagnosed with asthma, but her symptoms have not responded to a combined inhaled corticosteroid and long-acting bronchodilator. On physical examination, her respiratory rate is 16 breaths/min, pulse is 85 beats/min, blood pressure is 110/65, and her oxygen saturation on room air is 96%. She has scattered inspiratory crackles anteriorly with no wheeze. The remainder of her physical examination is unremarkable. Chest radiography shows scattered mid and upper lung interstitial markings, as well as possible hilar adenopathy. CT scan of the chest with IV contrast shows diffuse interstitial infiltrates in a peribronchovascular distribution, as well as a bilateral 2.5-cm hilar lymph nodes. Which of the following would be the best way to diagnose the cause of her lung disease?

A. Bronchoscopy with transbronchial biopsy and endobronchial ultrasound-guided transbronchial needle biopsy of hilar nodes
B. Pleuroscopy with pleural biopsy
C. Mediastinoscopy with biopsy of lymph nodes
D. Transthoracic needle biopsy of the lung parenchyma
E. Video-assisted thoracoscopic surgery with parenchymal lung biopsy

V-13. A 24-year-old woman is seen for a complaint of shortness of breath and wheezing. She notes the symptoms to be worse when she has exercised outdoors and is around cats. She has had allergic rhinitis in the spring and summer for many years and suffered from eczema as a child. On physical examination, she is noted to have expiratory wheezing. Her pulmonary function tests demonstrate an FEV_1 of 2.67 (79% predicted), FVC of 3.81 L (97% predicted), and an FEV_1/FVC ratio of 70% (86% predicted). After administration of albuterol, the FEV_1 increases to 3.0 L (12.4%). Which of the following statements regarding the patient's disease process is true?

A. Confirmation of the diagnosis will require methacholine challenge testing.
B. Mortality due to the disease has been increasing over the last decade.
C. The most common risk factor in individuals with the disorder is genetic predisposition.
D. The prevalence of the disorder has not changed in the last several decades.
E. The severity of the disease does not vary significantly within a given patient with the disease.

V-14. A 38-year-old woman is brought to the emergency department for status asthmaticus. She rapidly deteriorates and dies of her disease. All of the following pathologic findings would likely be seen in this individual EXCEPT:

A. Infiltration of the airway mucosa with eosinophils and activated T lymphocytes
B. Infiltration of the alveolar spaces with eosinophils and neutrophils
C. Occlusion of the airway lumen by mucus plugs
D. Thickening and edema of the airway wall
E. Thickening of the basement membrane of the airways with subepithelial collagen deposition

V-15. Which of the following patients is appropriately diagnosed with asthma?

A. A 24-year-old woman treated with inhaled corticosteroids for cough and wheezing that has persisted for 6 weeks following a viral upper respiratory infection
B. A 26-year-old man who coughs and occasionally wheezes following exercise in cold weather
C. A 34-year-old woman evaluated for chronic cough with an FEV_1/FVC ratio of 68% with an FEV_1 that increases from 1.68 L (52% predicted) to 1.98 L (61% predicted) after albuterol (18% change in FEV_1)
D. A 44-year-old man who works as a technician caring for the mice in a medical research laboratory and complains of wheezing, shortness of breath, and cough that are most severe at the end of the week
E. A 60-year-old man who has smoked two packs of cigarettes per day for 40 years who has dyspnea and cough and who has airway hyperreactivity in response to methacholine

V-16. Which of the following regarding the epidemiology of asthma is true?

A. Air pollution has not been convincingly shown to impact the prevalence of asthma in a given population.
B. Atopy is the most important risk factor in developing asthma.
C. The incidence of asthma is decreasing in developing countries.
D. There is a clearly established link between early childhood viral infections and the development of asthma.
E. Vitamin D deficiency has been shown to be an important risk factor for asthma.

V-17. A 32-year-old female was diagnosed with asthma 3 years ago in the setting of a reduced FEV_1, and reduced FEV_1/FVC ratio that both improved with bronchodilation. She in general has had mild symptoms, and has never needed to take oral corticosteroids or go to the emergency department for a severe exacerbation. She has been taking a short-acting β-agonist (SABA) inhaler for symptom relief. She normally takes her SABA one to two times per month but has noticed that she has recently needed to take it up to two to three times per week. This occasionally happens in the spring time when her seasonal allergies flare. During your office visit she is comfortable appearing, speaking in full sentences, and in no apparent distress. You appreciate occasional expiratory wheezes and scattered rhonchi on examination. What would be the most appropriate next step in her management at this point?

A. Check a complete blood count with differential and an IgE level
B. Obtain a chest radiograph to look for an acute infection
C. Obtain a full set of pulmonary function tests including spirometry, lung volumes, and diffusing capacity
D. Start a leukotriene antagonist
E. Start an inhaled corticosteroid

V-18. A 38-year-old woman was admitted to the medical intensive care unit with acute hypoxemic respiratory failure. She was well and healthy until 4 days prior when she abruptly began to feel ill with fevers, chills, bilateral pleuritic chest pain, and worsening shortness of breath. She has no significant past medical history but has suffered the recent death of her father following a car accident. In coping with his loss, she began smoking cigarettes again after a 15-year period of abstinence. She has been smoking up to two packs of tobacco daily. After she began to feel ill, she started taking acetaminophen and pseudoephedrine; otherwise, she takes no medications. On arrival in the emergency department, her oxygen saturation was 78% on room air. On a nonrebreather mask, the oxygen saturation increased to 92%. The vital signs are as follows: temperature 38.7°C (101.7°F), heart rate 122 beats/min, respiratory rate 28 breaths/min, and blood pressure 132/82. She appears in moderate respiratory distress. There are bilateral diffuse crackles. The cardiovascular examination shows a regular tachycardia without murmur. The jugular venous pressure is not elevated, and no edema is present. The abdomen is soft and not tender. No hepatosplenomegaly is present. Extremity and neurology examinations are normal. Chest radiograph shows diffuse bilateral infiltrates. Her echocardiogram shows normal left heart systolic and diastolic function. She is treated with ceftriaxone 1 g IV daily and azithromycin 500 mg IV daily. Over the course of the first 24 hours, the patient's clinical condition continues to deteriorate. She remains febrile, and she requires intubation and mechanical ventilation. The patient's ventilator is set on assist control with a rate of 28 beaths/min, tidal volume of 330 mL, FiO_2 of 0.8, and positive end-expiratory pressure of 12 cmH_2O. On these settings, her arterial blood gas values are pH 7.28, $PaCO_2$ 68 mmHg, and PaO_2 62 mmHg. Bronchoalveolar lavage is performed showing an elevated total cell count with 58% neutrophils, 12% lymphocytes, and 30% eosinophils. What is the best approach to the treatment of this patient at this time?

A. Consult thoracic surgery for surgical lung biopsy
B. Continue current IV antibiotic regimen while awaiting culture data
C. Initiate methylprednisolone 60 mg IV every 6 hours
D. Initiate oseltamivir 75 mg twice a day
E. Initiate therapy with trimethoprim/sulfamethoxazole IV with prednisone 40 mg twice a day

V-19. A 34-year-old woman seeks evaluation for a complaint of cough and dyspnea on exertion that has gradually worsened over 3 months. The patient has no past history of pulmonary complaints and has never had asthma. She started working in a pet store approximately 6 months ago. Her duties there include cleaning the reptile and bird cages. She reports occasional low-grade fevers but has had no wheezing. The cough is dry and non-productive. Before 3 months ago, the patient had no limitation of exercise tolerance, but now she reports that she gets dyspneic climbing two flights of stairs. On physical examination, the patient appears well. She has an oxygen saturation of 95% on room air at rest but desaturates to 89% with ambulation. Temperature is 37.7°C (99.8°F). The pulmonary examination is unremarkable. No clubbing or cyanosis is present. The patient has a normal chest radiogram. A high-resolution chest CT shows diffuse ground-glass infiltrates in the lower lobes with the presence of centrilobular nodules. A transbronchial biopsy shows an interstitial alveolar infiltrate of plasma cells, lymphocytes, and occasional eosinophils. There are also several loose noncaseating granulomas. All cultures are negative for bacterial, viral, and fungal pathogens. Which of the following is the most likely diagnosis?

A. Aspergillosis
B. Hypersensitivity pneumonitis
C. Nonspecific interstitial pneumonitis related to collagen vascular disease
D. Psittacosis
E. Sarcoidosis

V-20. What treatment do you recommend for the patient described in question V-19?

A. Amphotericin
B. Doxycycline
C. Glucocorticoids
D. Glucocorticoids plus azathioprine
E. Glucocorticoids plus removal of antigen

V-21. A 23-year-old male with cystic fibrosis has had an increase in the number of respiratory exacerbations over the last year, despite good compliance with airway clearance techniques and treatment with several rounds of antibiotics for chronic pseudomonas colonization. On examination in your office he has scattered wheezes over his anterior lung fields, as well as bibasilar crackles with rhonchi. CT of the chest reveals extensive upper lobe bronchiectasis with mucus plugging as well as scattered areas of bronchiolitis. In addition to repeat sputum cultures to look for new bacterial and atypical mycobacterial infections, which of the following tests would be indicated at this time?

A. Arterial blood gas analysis
B. Bronchoscopy with bronchoalveolar lavage
C. CT angiogram to look for pulmonary embolism
D. Exhaled breath sampling for nitric oxide
E. Serum IgE level

V-22. A 42-year-old female with a long-standing history of poorly controlled asthma requiring frequent rounds of oral corticosteroids presents to urgent care with a complaint of recent difficulty walking. She reports no recent change in her respiratory symptoms. Her symptoms began about 48 hours ago while walking in the grocery store. On review of systems she has had intermittent low-grade fevers and fatigue over the last several months. On examination she has difficulty in dorsiflexing her left foot. She also has numbness over her lateral calf and dorsum of her foot that spares the pinky toe and outside edge of the foot. Her lung examination is notable for occasional expiratory wheezes. Which of the following is the most likely diagnosis?

A. Acute trauma
B. Acute embolic stroke involving the right motor cortex
C. Compartment syndrome of the lower leg secondary to rhabdomyolysis
D. Compression of the peroneal nerve from habitually crossing of the legs
E. Mononeuritis of the peroneal nerve related to a previously undiagnosed eosinophilic granulomatosis with polyangiitis

V-23. A 75-year-old man is evaluated for a new left-sided pleural effusion and shortness of breath. He worked as an insulation worker at a shipyard for more than 30 years and did not wear protective respiratory equipment, retiring at the age of 60. He has a 50 pack-year history of tobacco with known moderate chronic obstructive pulmonary disease (FEV_1 55% predicted) and a history of myocardial infarction 10 years previously. His current medications include aspirin, atenolol, benazepril, tiotropium, and albuterol. His physical examination is consistent with a left-sided effusion with dullness to percussion and decreased breath sounds occurring over half of the hemithorax. On chest x-ray, there is a moderate left-sided pleural effusion with bilateral pleural calcifications and left apical pleural thickening. No lung mass is seen. A chest CT confirms the findings on chest x-ray and also fails to show a mass. There is compressive atelectasis of the left lower lobe. A thoracentesis is performed demonstrating an exudative effusion with 65% lymphocytes, 25% mesothelial cells, and 10% neutrophils. Cytology does not demonstrate any malignancy. Which of the following statements regarding the most likely cause of the patient's effusion or causative condition is true?

A. Cigarette smoking increases the likelihood of developing the condition.
B. Death in this disease is usually related to diffuse metastatic disease.
C. Exposure to the causative agent can be as brief as 1–2 years, and latency to expression of disease may be as great as 40 years.
D. Repeated pleural fluid cytology will most likely lead to a definitive diagnosis.
E. Therapy with a combination of surgical resection with adjuvant chemotherapy significantly improves long-term survival.

V-24. A 53-year-old man is seen in the emergency department with sudden-onset fever, chills, malaise, and shortness of breath but no wheezing. He has no significant past medical history and is a farmer. Of note, he worked earlier in the day stacking hay. Posteroanterior and lateral chest radiography shows diffuse bilateral alveolar infiltrates. Which organism is most likely to be responsible for this presentation?

A. *Nocardia asteroides*
B. *Histoplasma capsulatum*
C. *Cryptococcus neoformans*
D. *Actinomyces* species
E. *Aspergillus fumigatus*

V-25. A 44-year-old female presents with worsening shortness of breath over the last 6 months. She has a nonproductive cough but denies any fevers or weight loss. She is a non-smoker. Pulmonary function testing reveals a mixed obstructive, restrictive pattern, with a moderate reduction in her diffusing capacity. Chest radiograph reveals diffuse peribronchial interstitial infiltrates with some degree of mediastinal adenopathy. A bronchoscopy is performed. Bronchoalveolar lavage is negative for infection, but transbronchial biopsies show well-formed, noncaseating granulomas. Which of the following historical detail would lead you to question the presumptive diagnosis of sarcoidosis?

A. Her father was a steel worker, and she regularly washed his work uniform when she was a young girl.
B. She is a farmer and regularly works in a grain silo.
C. She makes stained glass windows in her spare time, and solders her own frames.
D. She works in a textile factory.
E. She works on the assembly line in an electronics factory.

V-26. A 58-year-old quarry worker presents for evaluation because of an abnormal chest radiograph that was obtained by his primary care physician to investigate a chronic cough. The radiograph shows poorly defined upper lobe nodules, as well as enlarged hilar lymph nodes with eggshell calcifications. A purified protein derivative (PPD) was placed by the primary care physician, and it is positive in your office 2 days later. Which of the following is likely true about this patient?

A. False-positive PPDs are common in patients exposed to silicate dust.
B. The patient likely has active pulmonary tuberculosis (TB) and needs to be isolated immediately.
C. The patient likely has invasive aspergillosis as the cause of his lung disease.
D. The patient likely has latent TB and given the possibility of underlying silicosis he should be treated for a longer period of time.
E. The patient needs an urgent surgical biopsy to exclude active TB and diagnose the cause of the lung disease.

V-27. A 51-year-old woman presents complaining of a daily cough productive of thick green sputum. The cough is worse when she first wakes in the morning. At this time, there are occasionally streaks of blood in the sputum. Her cough began about 7 years ago and has been progressively worse with production of increasing volume of sputum. She currently estimates that she brings up about half a cup of sputum daily. She reports frequently requiring antibiotics for both lower respiratory tract infections as well as sinus infections. Bilateral coarse crackles are heard in the lower lung zones. No clubbing is present. Pulmonary function tests demonstrate an FEV_1 of 1.68 L (53.3% predicted), FVC of 3.00 L (75% predicted), and FEV_1/FVC ratio of 56%. A sputum culture grows *Pseudomonas aeruginosa*. What test would you perform next in the evaluation of this patient?

A. Barium swallow study
B. Bronchoscopy
C. Chest radiography
D. High-resolution chest CT
E. Sweat chloride testing

V-28. A 45-year-old female presents to your office with intermittent cough productive of yellow sputum and mild dyspnea on exertion. She has been treated three times in the last 2 years for bronchitis with a course of oral antibiotics, and she feels better for several months after each episode. In the last few months she has noted increased fatigue and occasional wrist pain and swelling that is worse in the morning and relieved with ibuprofen. She has also noted that she has not been able to wear her contacts as frequently because her eyes have been dry. On examination of the chest she has scattered rhonchi and lower lobe rales. CT imaging shows mild lower lobe bronchiectasis with minimal interstitial thickening bilaterally. Which of the following tests is most likely to lead to the correct diagnosis?

A. Genetic testing for cystic fibrosis transmembrane conductance regulator mutations
B. Nasal mucosal biopsies
C. Serologies for rheumatoid factor and anti-Ro, anti-La antibodies
D. Sputum culture for tuberculosis
E. Sweat chloride testing

V-29. A 28-year-old woman is evaluated for recurrent lung and sinus infections. She recalls having at least yearly episodes of bronchitis beginning in her early teens. For the last 5 years, she states that she has been on antibiotics at least three times yearly for respiratory or sinus infections. She also reports that she has had difficulty gaining weight and has always felt short compared with her peers. On physical examination, the patient has a body mass index of 18.5 kg/m^2. Her oxygen saturation is 95% on room air at rest. Nasal polyps are present. Coarse rhonchi and crackles are heard in the bilateral upper lung zones. A chest radiograph shows bilateral upper lobe bronchiectasis with areas of mucus plugging. You are concerned about the possibility of undiagnosed cystic fibrosis. Which of the following tests would provide the strongest support for the diagnosis of cystic fibrosis in this individual?

A. DNA analysis demonstrating one copy of the F508del allele
B. Decreased baseline nasal potential difference
C. Presence of *Pseudomonas aeruginosa* on repeated sputum cultures
D. Sweat chloride values <30 mmol/L
E. Sweat chloride values >60 mmol/L

V-30. A 24-year old male with known cystic fibrosis (CF) presents to the clinic with worsening cough, sputum production, and shortness of breath over the last 3 weeks. Prior to this episode he has been doing fairly well, and has been compliant with his airway clearance regimen, which includes hypertonic saline nebulizers, inhaled dornase, and twice daily use of a flutter valve to aid with expectoration of sputum. You suspect that he has an acute CF exacerbation. Which of the following would be the most appropriate treatment?

A. Inhaled tobramycin to cover for likely *Pseudomonas*
B. IV ceftazidime and tobramycin to cover likely *Pseudomonas* infection
C. IV vancomycin and ceftriaxone to cover both methicillin-resistant *Staphylococcus aureus* infection as well as possible community-acquired pneumonia
D. Oral azithromycin, ethambutol, and rifampin to cover likely atypical mycobacterial infection
E. Oral prednisone and voriconazole to cover probable allergic bronchopulmonary aspergillosis

V-31. Which of the following best explains why patients with cystic fibrosis develop bronchiectasis?

A. Lack of functional cystic fibrosis transmembrane conductance regulator (CFTR) at the apical plasma membrane of epithelial cells leads to a depleted pericellular fluid layer, which in turn leads to ciliary dysfunction and failure to clear mucus.
B. Lack of functional CFTR in macrophages leads to ineffective immune surveillance and recurrent airway infection.
C. Lack of functional CFTR in type 2 epithelial cells impairs surfactant homeostasis and leads to airway fibrosis and remodeling.
D. Lack of functional CFTR leads to impaired migration of bronchoalveolar stem cells during embryogenesis leading to abnormal airway architecture, which predisposes to recurrent infection.
E. Liver dysfunction from obstruction of intrahepatic bile ducts leads to relative immunodeficiency and recurrent infection.

V-32. A 69-year-old man with chronic obstructive pulmonary disease (COPD) has been admitted to the hospital three times over the last year for COPD exacerbations. He has daily cough with sputum production and an FEV_1 of 45% predicted. He previously smoked a pack of cigarettes daily for 50 years, quitting 1 year ago. His oxygen saturation on room air is 91%. Which of the following treatments is most likely to decrease the frequency of his exacerbations?

A. Azithromycin 250 mg three times weekly
B. Continuous oxygen at 2 L/min
C. Nocturnal bilevel positive airway pressure with an inspiratory pressure of 18 cmH_2O and expiratory pressure of 12 cmH_2O
D. Roflumilast 500 μg daily
E. Theophylline 300 mg daily

V-33. A 56-year-old woman is admitted to the intensive care unit with a 4-day history of increasing shortness of breath and cough with copious sputum production. She has known severe chronic obstructive pulmonary disease with an FEV_1 of 42% predicted. On presentation, she has a room air blood gas with a pH of 7.26, $PaCO_2$ of 78 mmHg, and PaO_2 of 50 mmHg. She is in obvious respiratory distress with use of accessory muscles and retractions. Breath sounds are quiet with diffuse expiratory wheezing and rhonchi. No infiltrates are present on chest radiograph. Which of the following therapies has been demonstrated to have the greatest reduction in mortality rate for this patient?

A. Administration of inhaled bronchodilators
B. Administration of IV glucocorticoids
C. Early administration of broad-spectrum antibiotics with coverage of *Pseudomonas aeruginosa*
D. Early intubation with mechanical ventilation
E. Use of noninvasive positive-pressure ventilation

V-34. A 63-year-old man with a long history of cigarette smoking comes to see you for a 4-month history of progressive shortness of breath and dyspnea on exertion. The symptoms have been indolent, with no recent worsening. He denies fever, chest pain, or hemoptysis. He has a daily cough of 3–6 tablespoons of yellow phlegm. The patient says he has not seen a physician for over 10 years. Physical examination is notable for normal vital signs, a prolonged expiratory phase, scattered rhonchi, elevated jugular venous pulsation, and moderate pedal edema. Hematocrit is 49%. Which of the following therapies is most likely to prolong his survival?

A. Atenolol
B. Enalapril
C. Oxygen
D. Prednisone
E. Theophylline

V-35. A 65-year-old male with known chronic obstructive pulmonary disease presents to the clinic for a routine checkup. His symptoms have been stable on a daily long-acting antimuscarinic inhaler (tiotropium), and occasional albuterol. He has not had an exacerbation in the last 2 years. His FEV_1/FVC ratio is 60%, and his FEV_1 is 60% predicted. He unfortunately continues to smoke half a pack of cigarettes per day. He exercises three times a week on a treadmill for 30 minutes. Which of the following would be most effective management strategy at this point in time?

A. Addition of a long-acting β-agonist
B. Addition of an inhaled corticosteroid twice daily
C. Assessment for nocturnal hypoxemia
D. Referral to pulmonary rehabilitation
E. Smoking cessation counseling and consideration of pharmacologic therapy with varenicline

V-36. A 40-year-old presents to the clinic with 6 months of intermittent cough and sputum production, and worsening dyspnea on exertion. He has been treated at an urgent care center twice in the last year for bronchitis. He smokes about 1 pack of cigarettes per day and has done so for the last 20 years. Pulmonary function testing reveals an FEV_1/FVC ratio of 50%, with an FEV_1 of 45% predicted. CT of the chest reveals panacinar emphysema with slightly worse disease in the lower lobes. What would be the next step in management of this patient?

A. Careful environmental history to better understand possible exposure risk to airway irritants and toxins
B. Genetic testing for cystic fibrosis
C. Sputum culture to rule out atypical mycobacterial infection
D. Testing for alpha-1 antitrypsin levels
E. Ventilation-perfusion scanning to look for chronic thromboembolic disease

V-37. A 62-year-old man is evaluated for dyspnea on exertion that has progressively worsened over a period of 10 months. He has a 50 pack-year history of tobacco, quitting 10 years ago. On physical examination, has a resting oxygen saturation of 94%. After ambulation of 100 m, his oxygen saturation drops to 84%. He requires oxygen at 3 L/min to maintain his saturation at greater than 90% with ambulation. His lung examination shows diffuse end-inspiratory crackles throughout both lungs. His total lung capacity is 72% predicted, residual volume is 68% predicted, and diffusing capacity is 60% predicted. The chest CT is shown in Figure V-37. Serologic workup for autoimmune disease is unremarkable, and thorough history yields no exposures that would lead to these findings. You suspect idiopathic pulmonary fibrosis. What is the expected finding on surgical pathology?

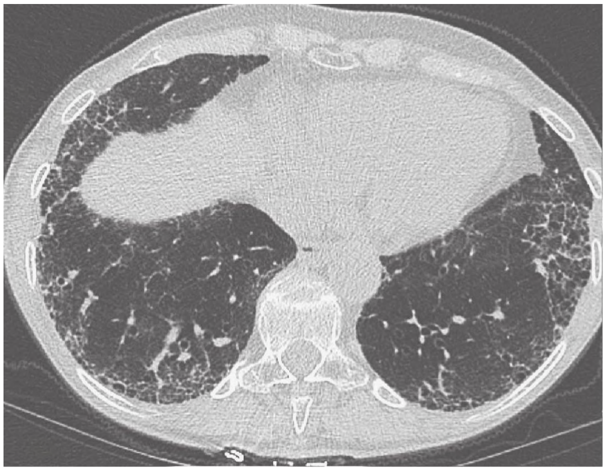


FIGURE V-37

A. Desquamative interstitial pneumonia
B. Diffuse alveolar damage
C. Loosely organized granulomatous inflammation and fibrosis
D. Nonspecific interstitial pneumonia
E. Usual interstitial pneumonia

V-38. What is the recommended treatment for the patient in question IV-37?

A. Azathioprine 125 mg daily plus prednisone 60 mg daily.
B. Cyclophosphamide 100 mg daily.
C. Nintedanib 150 mg twice a day.
D. Prednisone 60 mg daily.
E. No therapy is effective for treatment of idiopathic pulmonary fibrosis.

V-39. A 56-year-old woman presents for evaluation of dyspnea and cough for 2 months. During this time, she has also had intermittent fevers, malaise, and a 5.5-kg (12-lb) weight loss. She denies having any ill contacts and has not recently traveled. She works as a nurse, and a yearly purified protein derivative test performed 3 months ago was negative. She denies any exposure to organic dusts and does not have any birds as pets. She has no other exposures and no autoimmune symptoms. She takes no medications regularly. On physical examination, diffuse inspiratory crackles and squeaks are heard. A CT scan of the chest reveals patchy alveolar infiltrates and bronchial wall thickening. Pulmonary function testing reveals mild restriction. She undergoes a surgical lung biopsy. The pathology shows granulation tissue filling the small airways, alveolar ducts, and alveoli. The alveolar interstitium has chronic inflammation and organizing pneumonia. What is the most appropriate therapy for this patient?

A. Azathioprine 100 mg daily
B. Nintedanib 150 mg twice daily
C. Pirfenidone 2403 mg daily
D. Prednisone 1 mg/kg daily
E. Referral for lung transplantation

V-40. A 37-year-old female presents with several months of dry cough, with worsening dyspnea on exertion. She is a non-smoker. In addition to her respiratory complaints, she notes worsening fatigue, intermittent low-grade fevers, and aches in her thighs and lower back. She has a history of Raynaud syndrome in the past and also notes severe dry skin with cracking on the sides of her thumbs and index fingers over the last month that she attributes to doing the dishes more frequently at home. Chest CT reveals diffuse subpleural, symmetric, ground glass, and reticular opacities with perhaps some early traction bronchiectasis at the bases. Which of the following would most likely yield the correct diagnosis?

A. Bronchoscopy with bronchoalveolar lavage and transbronchial biopsies
B. Purified protein derivative skin testing
C. Serologies for anti-synthetase antibodies including Jo-1
D. Serum precipitins against common environmental exposures such as thermophilic bacteria and bird antigens
E. Video-assisted thoracoscopic lung biopsy

V-41. A 54-year-old male presents with worsening cough and exertional dyspnea over the last 2 months. He currently smokes 1.5 packs of cigarettes per day and has done so for 30 years. His pulmonary function tests show a normal FEV_1/FVC ratio, a total lung capacity that is 75% of predicted, and a diffusing capacity that is 60% of predicted. High-resolution CT of the chest shows diffuse centrilobular nodules and scattered ground-glass opacities. Which of the following treatments would be most likely effective for his interstitial lung disease?

A. Azathioprine
B. Nintedanib
C. Prednisone
D. Sirolimus
E. Smoking cessation

V-42. A 53-year-old man is admitted with fever and right pleuritic chest pain for 5 days. He has a history of alcohol dependence. On presentation, his temperature is 39.2°C, heart rate is 112 beats/min, blood pressure is 102/62, respiratory rate is 24 breaths/min, and SaO_2 is 92% on room air. He has absent breath sounds in the right lower chest with dullness to percussion and decreased tactile fremitus. Chest radiograph confirms a right lower lobe consolidation with associated effusion. The effusion is not free flowing. Initial thoracentesis demonstrates gross pus in the pleural space, and the Gram stain is positive for gram-positive cocci in pairs and chains. A large-bore chest tube is placed. Which of the following treatments should also be recommended in this patient to improve resolution of the empyema in this individual?

A. Immediate referral for decortication
B. Intrapleural instillation of alteplase 10 mg twice daily for 3 days
C. Intrapleural instillation of alteplase 10 mg plus deoxyribonuclease 5 mg twice daily for 3 days
D. Intrapleural instillation of deoxyribonuclease 5 mg twice daily for 3 days
E. Intrapleural instillation of streptokinase 250,000 IU

V-43. A 44-year-old woman with AIDS has acute hypoxemic respiratory failure due to *Pneumocystis jiroveci*. She is intubated and mechanically ventilated with the following settings: assist control, tidal volume 350 mL (6 mL/kg ideal body weight), FiO_2 1.0, respiratory rate 28 breaths/min, and positive end-expiratory pressure 12 cmH_2O. Her arterial blood gas values on these settings are as follows: pH 7.28, PaO_2 68 mmHg, and $PaCO_2$ 64 mmHg. Her inspiratory plateau pressure is 26 cmH_2O. You are called acutely to the bedside when her blood pressure abruptly drops to 70/40 mmHg. At the same time, the high-pressure alarms on the ventilator begin to alarm with peak airway pressures now registering at 55 cmH_2O. Breath sounds are inaudible on the right side and are clear on the left. What is the best course of action at this time?

A. Administer a fluid bolus to improve venous return.
B. Disconnect the patient from the ventilator to allow a full exhalation.
C. Place a large-bore needle into the right second anterior intercostal space to alleviate a tension pneumothorax.
D. Sedate the patient to achieve ventilator synchrony.
E. Suction the patient to remove obstructing mucus plugs.

V-44. A 28-year-old man presents to the emergency department with acute-onset shortness of breath and pleuritic chest pain on the right that began 2 hours previously. He is generally healthy and has no medical history. He has smoked one pack of cigarettes daily since the age of 18. On physical examination, he is tall and thin, with a body mass index of 19.2 kg/m^2. He has a respiratory rate of 24 breaths/min with an oxygen saturation of 95% on room air. He has slightly decreased breath sounds at the right lung apex. A chest x-ray demonstrates a 20% pneumothorax on the right. Which of the following statements is true regarding pneumothorax in this patient?

A. A CT scan is likely to show emphysematous changes.
B. If the patient were to develop recurrent pneumothoraces, thoracoscopy with pleural abrasion has a success rate of near 100% for prevention of recurrence.
C. Most patients with this presentation require tube thoracostomy to resolve the pneumothorax.
D. The likelihood of recurrent pneumothorax is about 25%.
E. The primary risk factor for the development of spontaneous pneumothorax is a tall and thin body habitus.

V-45. A 57-year-old man with a known history of congestive heart failure presents to the emergency department with increasing dyspnea and lower extremity edema. On examination he has an elevated jugular venous pressure and bilateral lower extremity pitting edema. He also has increased dullness to percussion, decreased tactile fremitus, and diminished breath sounds at his right base. Chest radiograph reveals a moderate right pleural effusion, a small left pleural effusion, and pulmonary vascular congestion. He is afebrile and denies any chest discomfort. His breathing improves with IV furosemide. Pleural fluid analysis from a right-sided thoracentesis reveals a pH of 7.42, lactate dehydrogenase of 280, pleural fluid protein of 4 mg/dL, and serum protein of 7.5 mg/dL. Based on these results, you recommend which of the following?

A. Continued management for congestive heart failure; the effusion is likely a transudate that has been misclassified as an exudate.
B. IV antibiotics for possible pneumonia and parapneumonic effusion.
C. Large bore chest tube placement on the right side with instillation of doxycycline to prevent fluid reaccumulation.
D. Thoracentesis on the left side to make sure that the left side is not also exudative.
E. Thoracoscopy and pleural biopsy to exclude malignancy or tuberculosis as the cause of the exudative effusion on the right side.

V-46. A 37-year-old man presents with 2 days of left-sided chest discomfort that is worse with deep breathing. He has been having low-grade fevers as well as a cough for about 4 days in total. Chest radiograph in the emergency department reveals a moderate-sized left-sided pleural effusion but no clear consolidation or signs of pneumonia. A thoracentesis reveals a pH of 7.35, lactate dehydrogenase of 400, serum protein of 7 mg/dL, and a pleural fluid protein of 4.5 mg/dL. Pleural fluid cultures and cytology are unrevealing. He is treated with empiric antibiotics, and after 2 days his chest pain and fevers resolve. Repeat chest radiograph shows that the pleural effusion is much smaller, although still present. What would be the most appropriate next step in management?

A. Chest CT with IV contrast to rule out pulmonary embolism
B. Follow-up in clinic in 1–2 weeks to make sure that he is continuing to improve
C. Repeat thoracentesis to check adenosine deaminase levels and mycobacterial cultures
D. Repeat thoracentesis to recheck pleural fluid cytology
E. Thoracoscopy and pleural biopsy to exclude malignancy

V-47. A 52-year-old woman from Indiana presents with worsening dyspnea on exertion and cough for a year. She denies dyspnea at rest. The cough is predominantly dry, but it is occasionally productive of a gritty mucus. Her past medical history is positive for hypertension and hypothyroidism. She takes benazepril and levothyroxine. She has primarily worked as a landscaper throughout her adult life. On physical examination, she appears in no distress. Her oxygen saturation is 95% on room air. Chest is clear to auscultation. Cardiovascular examination is unremarkable. She has no peripheral edema. The chest radiograph shows an old granuloma in the right lung and mediastinal calcifications. A CT scan is performed, which confirms the healed granuloma. Extensive mediastinal calcification is seen. The calcifications encase the superior vena cava and the right main-stem bronchus. An interferon-γ assay is negative. Which of the following statements regarding the patient's conditions is true?

A. A urine *Histoplasma* antigen test will be positive.
B. The most common cause of the condition is histoplasmosis or tuberculosis.
C. The patient should be referred to a surgical center specialized in the treatment of this condition.
D. Treatment with corticosteroids will improve the patient's condition.
E. Treatment with itraconazole or voriconazole will improve the patient's condition.

V-48. A 52-year-old woman is admitted to the hospital with lethargy and marked signs and symptoms of volume overload. She has a past medical history of morbid obesity with a body mass index of 52 kg/m^2, severe obstructive sleep apnea, hypertension, and type 1 diabetes mellitus. She is in generally poor health and has been noncompliant with her insulin as well as with continuous positive airway pressure (CPAP) as she reports claustrophobia. She cannot recall when she last used CPAP therapy. On physical examination, the patient is somnolent but arousable. Her vital signs are as follows: blood pressure 168/92, heart rate 92 beats/min, respiratory rate 14 breaths/min, afebrile, and SaO_2 82% on room air. Her SaO_2 increases to 92% on 6 L/min by nasal cannula, but her mental status becomes more lethargic. She has distant heart and lung sounds without crackles. There is 4+ edema bilateral to the thighs and onto the abdominal wall. Chest x-ray shows low lung volumes. Initial arterial blood gas values on 6 L/min nasal oxygen are pH 7.22, $PaCO_2$ 88 mmHg, and PaO_2 72 mmHg. Which of the following statements is true regarding the patient's condition?

A. Abnormalities of the *PHOX2b* gene are associated with this condition.
B. CPAP therapy alone is adequate for treatment of this patient.
C. Initial treatment of the condition should include intubation and mechanical ventilation given the patient's known intolerance of CPAP therapy.
D. Obstructive sleep apnea coexists with the diagnosis in less than 50% of cases.
E. Weight loss will lead to improvements in $PaCO_2$ over time.

V-49. A patient with mild amyotrophic lateral sclerosis is followed by a pulmonologist for respiratory dysfunction associated with his neuromuscular disease. Which of the following symptoms in addition to $PaCO_2$ ≥45 mmHg would necessitate therapy with noninvasive positive pressure ventilation for hypoventilation?

A. Orthopnea
B. Poor-quality sleep
C. Impaired cough
D. Dyspnea in activities of daily living
E. All of the above

V-50. A 57-year-old female with known chronic obstructive pulmonary disease presents to the emergency department with worsening shortness of breath over the last 3 days. Her family notes that she has been somewhat confused over the last 24 hours. On physical examination she is breathing 25 times per minute and using accessory muscles. She has diffuse wheezes bilaterally and a prolonged expiratory phase. Her oxygen saturation on room air is 87% and increases to 92% with 3 L of supplemental oxygen by nasal cannula. An arterial blood gas reveals a pH of 7.30, $PaCO_2$ of 75, and a PaO_2 of 65 on 3 L oxygen. Her serum bicarbonate is 30 mEq/dL and serum creatinine is normal. Which of the following best explains her current acid-base status?

A. A metabolic acidosis and a respiratory acidosis
B. A metabolic alkalosis with compensatory metabolic acidosis
C. An acute on chronic respiratory acidosis with a compensatory metabolic alkalosis
D. An acute respiratory acidosis
E. A chronic respiratory acidosis with a compensatory metabolic alkalosis

V-51. A 52-year-old man is evaluated for loud snoring and daytime fatigue. His wife urged him to come in for evaluation because his snoring has become increasingly disruptive over the last 2 years after he gained about 30 lb. She frequently sleeps in another room and reports that she has seen him stop breathing during sleep. During the day, he struggles to stay awake when he is in meetings or sitting at his computer, particularly after lunch. He has a 40-minute commute and has had to pull off the road due to feelings of sleepiness. He has a medical history of hypertension for the last 5 years and takes losartan 25 mg daily. He does not smoke and drinks one beer or a glass of wine daily. His father, who is 75 years old, uses a continuous positive airway pressure (CPAP) machine for obstructive sleep apnea and has also had a myocardial infarction. On physical examination, the patient appears well. He has a body mass index of 37.1 kg/m^2. When the patient opens his mouth, you can see most of his uvula, which appears somewhat edematous. Tonsillar tissue is visible and extends just beyond tonsillar pillars. The neck circumference is 43 cm. What is the next step in the evaluation and treatment of this patient?

A. Attended in-lab polysomnography
B. Home sleep study
C. Overnight oximetry
D. Referral for tonsillectomy
E. Treatment with autotitrating CPAP

V-52. Which patient below is most likely to have the breathing pattern seen on polysomnography as shown in Figure V-52?

A. A 6-year-old boy with poor school performance, snoring, and enlarged tonsils and adenoids.
B. A 36-year-old woman with a history of heroin addiction who is being treated with methadone maintenance therapy at a dose of 100 mg daily.
C. A 48-year-old man evaluated for loud snoring and excessive sleepiness with a body mass index of 36.8 kg/m^2.
D. A 52-year-old woman with a body mass index of 22 kg/m^2 complaining of frequent nocturnal awakenings in the setting of menopause; she does not snore.
E. A 68-year-old man with atrial fibrillation and ischemic cardiomyopathy with an ejection fraction of 15%; on examination, he has elevation of the jugular venous pressure.

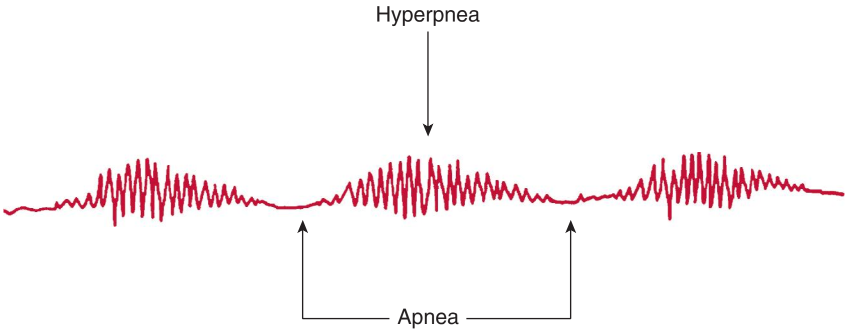


FIGURE V-52 Reproduced with permission from Grippi MA et al: *Fishman's Pulmonary Diseases and Disorders*, 5th ed. New York: McGraw Hill, 2015.

V-53. A 48-year-old man with a body mass index of 32 has recently been diagnosed with obstructive sleep apnea with an apnea-hypopnea index of 13 per hour. He does not have a history of snoring. He presents to the clinic for follow-up because he has tried wearing continuous positive airway pressure (CPAP) at home but has not felt comfortable with it. He asks if there are other potential treatment options for his sleep apnea. Which of the following would be a possible alternative therapy?

A. Bariatric surgery.
B. An oral appliance.
C. Supplementation oxygen.
D. Upper airway neurostimulation is the preferred treatment of mild sleep apnea in patients who have failed CPAP therapy.
E. Upper airway surgery such as uvulopalatopharyngoplasty is as effective as oral appliances.

V-54. A 47-year-old woman with idiopathic pulmonary arterial hypertension has failed medical therapy including oral agents and IV epoprostenol. She has advanced right heart failure with severe right ventricular dysfunction on echocardiography and a cardiac index of 1.7 L/min/m^2. She is referred for lung transplantation. Which of the following statements regarding lung transplantation in this case is true?

A. She will require heart-lung transplantation for her advanced right heart failure.
B. Idiopathic pulmonary arterial hypertension patients have worse 5-year survival than other transplant recipients.
C. Single-lung transplantation is the preferred surgical procedure for idiopathic pulmonary arterial hypertension.
D. Her own right ventricular function will recover after lung transplantation.
E. She is at risk for recurrent pulmonary arterial hypertension after lung transplantation.

V-55. A 63-year-old male with idiopathic pulmonary fibrosis (IPF) undergoes a double lung transplant. On postoperative day 2 he is still intubated. Over the course of the day he develops worsening hypoxemia and progressive bilateral infiltrates. His PaO_2/FiO_2 ratio is 180. He does not have any lower extremity edema, and his fluid status has been net even since the operation, with a good urine output. He is afebrile. A bedside echocardiogram shows normal left ventricular function with no pericardial effusion. Which of the following is the most likely cause of his hypoxia and respiratory failure?

A. Acute left heart failure from the stress of the transplant operation
B. Acute respiratory distress syndrome from an acute infection
C. Drug reaction from induction immunosuppression
D. Primary allograft dysfunction
E. Noncardiogenic pulmonary edema related to anesthesia during the surgery

V-56. A 38-year-old female with cystic fibrosis is 4 years out from a double lung transplant. She had an episode of mild primary allograft dysfunction immediately postoperatively, and has had two episodes of acute cellular rejection that were successfully treated with augmentation of her immunosuppression. She is currently on a combination of prednisone, tacrolimus, and mycophenolate. Three months ago she developed mild dyspnea on exertion and her FEV_1 dropped from her previous baseline of 85% predicted to 65% predicted. Which of the following findings on evaluation would suggest the diagnosis of bronchiolitis obliterans syndrome?

A. Fifty percent stenosis of her middle lobe bronchus just distal to the anastomotic site
B. Bronchoalveolar lavage cultures positive for *Aspergillus fumigatus* on 3/5 plates
C. Lymphocytic infiltrates surrounding her arterioles on transbronchial biopsy
D. New air trapping on expiratory CT without any clear infiltrates
E. New moderate restriction on pulmonary function testing

V-57. A 48-year-old woman is admitted to the intensive care unit with acute respiratory distress syndrome and shock due to ascending cholangitis. Her Acute Physiology and Chronic Health Evaluation Score (APACHE II) is 19 at 24 hours. Which statement best describes the performance of severity of illness scoring systems in predicting outcomes for a patient such as the one described?

A. The APACHE II score and other severity of illness tools are useful for informing clinical research in critical illness, especially regarding severity of illness in patients enrolled in clinical trials.
B. The APACHE II score is an important predictor of individual mortality when directly applied to patient care.
C. The APACHE II score should be used to guide therapy in this patient.
D. The Simplified Acute Physiology Score would perform better at predicting mortality than the APACHE II score.
E. All of the above are true.

V-58. A 42-year-old man is admitted to the intensive care unit after an automobile accident. He suffered a compound fracture of the femur and also had internal bleeding from a ruptured spleen and liver hematoma. He has undergone splenectomy and fixation of the femur fracture. He is intubated and sedated following surgery. His hemoglobin after surgery is 5.2 g/dL. His oxygen saturation is 92%, and his PaO_2 is 72 mmHg on FiO_2 of 0.6. A pulmonary artery catheter was placed during surgery. His cardiac output is 7.8 L/min. A lactate level is 4.8 mmol/L. Which of the following is the least important factor affecting oxygen delivery in this patient?

A. Cardiac output
B. Hemoglobin concentration
C. PaO_2
D. SaO_2

V-59. A 62-year-old female is admitted to the intensive care unit for management of sepsis secondary to a urinary tract infection. Over the course of the first 6 hours in the intensive care unit she develops worsening respiratory distress and is ultimately intubated for progressive hypoxia and increased work of breathing. Just before intubation her heart rate is 115/min and her blood pressure is 115/75. Immediately after intubation, her heart rate increases to 125 and her blood pressure drops to 85/60. Which of the following is *least* likely to cause the acute drop in blood pressure in this patient?

A. Gastrointestinal bleeding
B. Positive pressure ventilation
C. Reduction in respiratory distress after intubation
D. Right main-stem intubation
E. Sedative medications

V-60. A 75-year-old male was intubated for hypoxemia respiratory failure in the setting of a community-acquired pneumonia. He is now on day 6 of mechanical ventilation and has been weaned to an FiO_2 of 0.30. He passed the criteria for a spontaneous breathing trial. All of the following would predict failure to successfully wean from mechanical ventilation during a spontaneous breathing trial EXCEPT:

A. Oxygen saturation <90%
B. Pulse rate >140 beats/min
C. Respiratory rate <25 breaths/min
D. Systolic blood pressure >180
E. Systolic blood pressure <90

V-61. A 68-year-old man is admitted to the intensive care unit with fevers, hypotension, and hypoxemia. He has felt ill for the last 2 to 3 days with progressive dyspnea at home. He has a history of chronic obstructive pulmonary disease, coronary artery disease requiring three-vessel coronary artery bypass surgery, and type 2 diabetes mellitus. He continues to smoke a pack of cigarettes daily and also drinks a six-pack of beer daily. On presentation, his room air oxygen saturation is 79%. With a nonrebreather mask, his oxygen saturation remains at 87%. His blood pressure is 74/40, and heart rate is 124 beats/min. After fluid bolus, his blood pressure remains low at 86/53. His chest radiograph is shown in Figure V-61. Within 12 hours after admission, blood cultures are positive for *Streptococcus pneumoniae*. He received his first dose of antibiotics in the emergency department and remains on treatment with ceftriaxone and moxifloxacin. He is intubated, sedated, and currently on vasopressor support. His blood gas after intubation is pH 7.28, $PaCO_2$ 52 mmHg, and PaO_2 64 mmHg on FiO_2 0.8. Which of the following best identifies the patient's diagnosis?

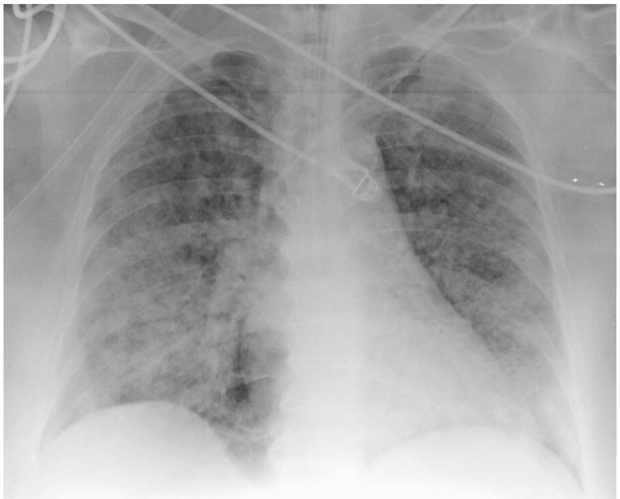


FIGURE V-61

A. Acute interstitial pneumonia
B. Mild acute respiratory distress syndrome
C. Moderate acute respiratory distress syndrome
D. Multilobar community-acquired pneumonia
E. Severe acute respiratory distress syndrome

V-62. If a lung biopsy were to be taken 4 days after admission in the patient in questions V-61, which statement correctly identifies the expected findings?

A. Diffuse alveolar damage with hyaline membranes and protein-rich edema fluid in alveoli
B. Extensive eosinophil-rich infiltrate with protein-rich edema fluid
C. Extensive fibrosis of the alveolar ducts with development of bullae
D. Homogeneous infiltrate of neutrophils and leukocytes affecting all alveolar spaces
E. Proliferation of type II pneumocytes and presence of a lymphocyte-rich pulmonary infiltrate

V-63. A 48-year-old woman is admitted to the surgical intensive care unit (ICU) following a motor vehicle accident. She has suffered a concussion, fractures of ribs 4 through 8 on the left with a hemopneumothorax, and a lacerated spleen that required splenectomy. During the surgery to remove her spleen, she required transfusion of 6 units of packed red blood cells, 6 units of platelets, and 4 units of fresh frozen plasma. On admission to the ICU after surgery, she remains intubated and sedated. A chest tube is in place on the left. Her chest radiograph shows diffuse bilateral infiltrates. The left lung has dense infiltrates, and there are also extensive infiltrates on the right. She is diagnosed with a left lung contusion and acute respiratory distress syndrome. She weighs 90 kg. She is 66 inches in height. Her ideal body weight is 59 kg. Her oxygen saturation on an FiO_2 of 1.0 is 92% with an arterial blood gas showing a pH of 7.28, $PaCO_2$ of 48 mmHg, and PaO_2 of 68 mmHg. Which of the following is the best initial tidal volume in this patient?

A. 236 mL
B. 354 mL
C. 472 mL
D. 540 mL
E. 590 mL

V-64. A 32-year-old female is admitted to the intensive care unit with respiratory failure secondary to influenza pneumonia. She is intubated and sedated. Her initial ventilator settings are volume control with a respiratory rate of 35, tidal volume (TV) of 420 mL, FiO_2 of 0.60, and positive end-expiratory pressure (PEEP) of 12 cmH_2O. Her blood gas after 30 minutes on those settings reveals a pH of 7.21, PCO_2 of 65, and PaO_2 of 65. Her plateau pressure is 22 cmH_2O. Her blood pressure is 110/65, her heart rate is 105 beats/min, and her saturation is 91%. Her ideal body weight is 70 kg. What is the most appropriate next step in terms of ventilator management?

A. Increase FiO_2 to 80%
B. Increase PEEP to 14 cmH_2O
C. Increase respiratory rate to 40 breaths/min
D. Increase TV to 480 mL
E. Maintain current settings

V-65. A 75-year-old female is admitted to the intensive care unit with mesenteric ischemia. She undergoes emergent surgery to remove a section of necrotic small bowel. On postoperative day 1 she develops worsening shortness of breath and hypoxia. On chest radiograph she has bilateral alveolar infiltrates with no signs of fluid overload on examination. All of the following treatments have supporting evidence for efficacy in early acute respiratory distress syndrome EXCEPT:

A. Early use of paralytic agents
B. Fluid restriction
C. Glucocorticoids
D. Low tidal volume ventilation
E. Prone positioning

V-66. In which of the following situations would noninvasive mechanical ventilation considered to be contraindicated?

A. Acute exacerbation of chronic obstructive pulmonary disease (COPD)
B. Acute hypoxemic respiratory failure in an individual with acute respiratory distress syndrome
C. Acute myocardial infarction
D. Decompensated systolic heart failure without acute myocardial ischemia
E. After extubation in an individual who had been intubated for COPD

V-67 to V-70. Match the mode of ventilation with its description.

V-67. Assist-control ventilation

V-68. Intermittent mandatory ventilation

V-69. Pressure control ventilation

V-70. Pressure support ventilation

A. This mode of ventilation is time triggered and time cycle and pressure limited. The tidal volume and inspiratory flow rate are dependent on lung compliance.
B. This mode of ventilation provides a set minute ventilation based on respiratory rate and tidal volume. Spontaneous breaths above the set respiratory rate may be supported in a pressure mode.
C. This mode of ventilation is the most common mode of mechanical ventilation. Each breath, whether triggered by the patient or the ventilator, provides a prespecified tidal volume.
D. This mode of ventilation is patient triggered, flow cycled, and pressure limited. Use of this mode of ventilation requires a patient to be spontaneously breathing.

V-71. A 75-year-old woman is admitted to the medical intensive care unit with hypoxic respiratory failure from a community-acquired pneumonia. You diagnose acute respiratory distress syndrome based on the presence of bilateral infiltrates, hypoxemia, and the absence of heart failure. She receives sedation and neuromuscular blockade to facilitate intubation. The respiratory therapist asks you which mode of ventilation to use after intubation. Which of the following would be the most appropriate mode in this patient?

A. Assist-control ventilation with a tidal volume of 6 cc/kg ideal body weight
B. Extracorporeal membrane oxygenation
C. Continuous positive airway pressure to minimize the risk of barotrauma
D. Pressure-controlled ventilation to minimize elevations in peak airway pressure
E. Pressure support ventilation to improve patient-ventilator synchrony

V-72. The patient from question V-71 has been treated for her pneumonia and has slowly improved over the last 7 days. You are considering a spontaneous breathing trial (SBT) to help decide if she might be ready for extubation. Which of the following would be a contraindication to an SBT?

A. Acute kidney injury
B. FiO_2 0.40
C. History of a traumatic intubation and concern for vocal cord injury
D. New and worsening hypertension with a systolic blood pressure of 220 as sedation has been weaned
E. Positive end-expiratory pressure of 8 cmH_2O

V-73. All of the following statements regarding the pathophysiology of shock are true EXCEPT:

A. Hypotension inhibits the vasomotor center, resulting in decreased adrenergic output and increased vagal activity.
B. Metabolic changes, including glycolysis and lipolysis, raise extracellular osmolarity, leading to an osmotic gradient that increases interstitial volume at the expense of intracellular fluid volume.
C. Mitochondrial dysfunction and uncoupling of oxidative phosphorylation lead to decreased adenosine triphosphate levels and a consequent accumulation of lactate and other reactive oxygen species.
D. Proinflammatory mediators stimulated by the innate immune system contribute significantly to multiple organ dysfunction and failure in shock.
E. Severe stress or pain causes increased release of adrenocorticotropic hormone, subsequently increasing cortisol levels to increase gluconeogenesis, decreasing peripheral uptake of glucose and amino acids, and enhancing lipolysis.

V-74. A 35-year-old previously healthy male is brought to the emergency department by his sister after he was stung by a wasp at a family picnic. Shortly after the sting he developed facial swelling, shortness of breath, and altered mental status. On arrival his blood pressure is 72/45 with a heart rate of 135 beats/min. He is saturating 92% on room air with a respiratory rate of 24 breaths/min. He is afebrile. Which of the following would be the expected findings on a pulmonary artery catheter?

	Central Venous Pressure and Pulmonary Capillary Wedge Pressure	Cardiac Output	Systemic Vascular Resistance	Venous O_2 Saturation
A.	↓	↓	↑	↓
B.	↑	↓	↑	↓
C.	↓	↑	↓	↓
D.	↓	↓↑	↓↑	↓
E.	↓	↓	↓	↓

V-75. All of the following statements regarding the epidemiology of sepsis and septic shock are true EXCEPT:

A. Gram-positive bacteria are the most commonly isolated causative organisms in sepsis syndromes.
B. In individuals with septic shock, blood cultures are positive in 40–70% of cases.
C. Most cases of sepsis occur in individuals with significant underlying illness.
D. Respiratory infections are the most common cause of sepsis syndromes.
E. The annual incidence of severe sepsis has increased over the last 30 years with currently over 750,000 cases yearly.

V-76. Despite appropriate antibiotic therapy and supportive care, the mortality related to sepsis remains high with 40–60% of patients with septic shock dying within 30 days. Multiple therapies have been attempted to improve this mortality, but many of these have been found to be ineffective after initially promising results. Examples of these ineffective therapies include all of the following EXCEPT:

A. Activated protein C
B. Erythrocyte transfusions to maintain a hemoglobin level >7 g/dL
C. Insulin therapy to achieve tight glucose control (100–120 mg/dL)
D. Performance of adrenocorticotropin hormone stimulation tests for adrenal insufficiency
E. Tissue factor pathway inhibitor

V-77. A 63-year-old female with a history of heavy alcohol use is brought to the emergency department by her sister with altered mental status and fever. Her sister reports that she has been complaining of a productive cough with pleuritic chest pain and fever for the last 2 days. On examination her temperature is 39.5°C (103.1°F), pulse is 110 beats/min, blood pressure is 100/65, respiratory rate is 25 breaths/min, and oxygen saturation 90% on room air. She has dullness to percussion at her right base with increased tactile fremitus, crackles, and egophony. She is alert and oriented only to self but does not have any clear focal neurologic deficits. Chest radiograph reveals a dense right lower lobe consolidation. On initial laboratory testing she is noted to have a white blood cell count of 22,000/μL with 90% neutrophils. Her creatine is elevated to 1.4 (baseline 0.8). Which of the following best describes her current condition?

A. Mild sepsis
B. Sepsis
C. Septic shock
D. Severe sepsis
E. Systemic inflammatory response syndrome

V-78. A 36-year-old male presents to the emergency department with a fever of 39.5°C (101°F). He recently underwent an allogeneic bone marrow transplant for acute myelogenous leukemia, and he was discharged home to continue his recovery. His vital signs are notable for a pulse of 120 beats/min, respiratory rate of 22 breaths/min, blood pressure of 125/75, and an oxygen saturation of 98% on room air. He is flushed and uncomfortable appearing, but has no localizing findings with clear lungs, no obvious skin infection or rash, and no areas of tenderness or erythema. He has a right arm peripherally inserted central catheter line whose site is clean, dry, and intact without erythema or exudate. His initial labs show a white blood cell count of 2000 with an absolute neutrophil count of 420. Which of the following would be the most appropriate empiric antimicrobial regimen while you conduct additional investigations?

A. Aztreonam and vancomycin
B. Cefepime, tobramycin, vancomycin, and caspofungin
C. Ciprofloxacin and metronidazole
D. Meropenem and caspofungin
E. Piperacillin/tazobactam and vancomycin

V-79. A 19-year-old previously healthy man presents to the emergency department with 3 days of worsening dyspnea and fatigue. Approximately 2 weeks ago, he had typical upper respiratory type symptoms including cough, coryza, fevers to maximal 39.5°C (103.1°F), and muscle aches. On arrival to the emergency room today, he is awake and communicative, but notably dyspneic. His blood pressure is 88/75, resting heart rate is 112 beats/min, and pulse oximetry reports a saturation of 98% on room air. On physical examination, his jugular venous pulse is elevated to the mandible. He has faint rales in the bilateral lung bases and an S_3 gallop on auscultation. His limbs are cool to touch, though he has no peripheral edema. Electrocardiogram shows sinus tachycardia without ST or T wave changes. Laboratory studies demonstrate elevated creatinine and normal white blood cell, hemoglobin, and platelet counts. If a pulmonary artery catheter was placed, what hemodynamic data would be most likely obtained from this patient?

A. Elevated cardiac output
B. Elevated stroke volume
C. Reduced pulmonary arterial oxygen saturation
D. Reduced pulmonary capillary wedge oxygen saturation
E. Reduced systemic vascular resistance

V-80. You are called to the bedside acutely to see an 84-year-old woman who was admitted for upper respiratory infection symptoms 48 hours ago. On arrival to the hospital, her vital signs were normal except for mild resting tachypnea (20 breaths/min). Chest x-ray on admission was normal without infiltrates. Since arrival, she has been receiving as-needed acetaminophen for fever, 200 cc/h normal saline, azithromycin, and a cough suppressant. Tonight, her nurse noted that she was significantly more dyspneic and thus paged you for assessment. On your arrival to her room, she appears uncomfortable and is sitting upright in bed. Vital signs are temperature 37°C (98.6°F), heart rate 105 beats/min, blood pressure 165/95, and respiratory rate 28 breaths/min. You see a biphasic pulse that declines with inspiration near her mandible sitting upright. Auscultation discloses coarse crackles half-way up the lung fields. Review of her medication administration record shows that she recently took azithromycin 1 hour prior and that normal saline continues at its original rate. All of the following interventions are reasonable next treatment options EXCEPT:

A. Discontinue IV normal saline
B. IV furosemide 80 mg
C. IV morphine
D. STAT doses of cefepime and vancomycin
E. Sublingual nitroglycerin

V-81. A 74-year-old woman was admitted to the neurologic intensive care unit with decreased alertness that progressed to coma following a fall on an icy sidewalk. On physical examination, the patient is minimally responsive to painful stimuli. The left pupil is enlarged. Right Babinski is upgoing, and there is apparent weakness of the right side. An MRI scan is performed (Figure V-81). What is the etiology of the coma in this patient?

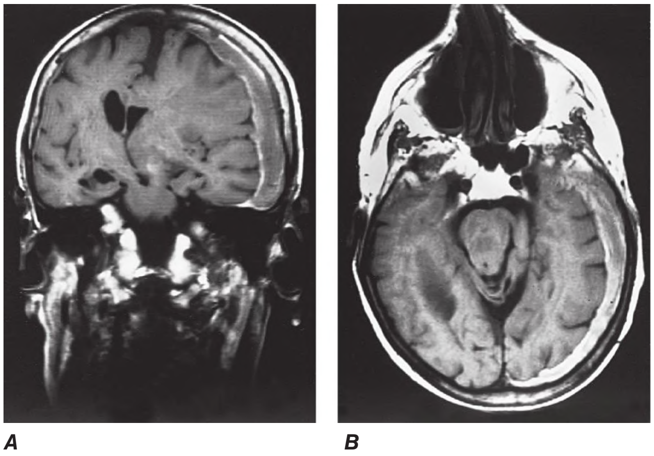


FIGURE V-81

A. Compression of the anterior and posterior cerebral arteries
B. Compression of the midbrain against the opposite tentorial edge
C. Compression of the opposite cerebral peduncle against the tentorial edge
D. Displacement of the cerebellar tonsils into the foramen magnum
E. Entrapment of the ventricular system causing hydrocephalus

V-82. A 48-year-old man was admitted to the intensive care unit with a large intracranial bleed following a motorcycle accident. On initial CT scan, there was midline shift and evidence of uncal herniation. At the scene of the accident, the patient was initially minimally responsive but has been totally unresponsive to all stimuli since admission. The patient was intubated by emergency medical services en route to the hospital. He has now been admitted for 24 hours. You believe the patient is brain dead. Which of the following contributes to the diagnosis of brain death?

A. Absence of pupillary light reflex
B. Apnea
C. Loss of oculovestibular reflexes
D. Unresponsiveness to all forms of stimulation
E. All of the above are criteria for assessment of brain death

V-83. A 73-year-old female with chronic alcoholic liver disease was admitted to the hospital for a urinary tract infection and suspected sepsis. You are called to see her overnight by her nurse who is concerned that she has become increasingly unresponsive over the course of the evening. On your arrival, she is lying in bed with the following vital signs: pulse 85 beats/min, blood pressure 135/90, respiratory rate 18 breaths/min, and oxygen saturation 94% on room air. On cranial nerve examination you notice that her eyes are deviated to the left. Which of the following lesions would explain these eye findings?

A. Hepatic encephalopathy
B. Left pontine hemorrhage
C. Right frontal lobe hemorrhage
D. Right frontal lobe seizure
E. Uncal herniation from a right-sided intracerebral hemorrhage

V-84. Which of the following statements regarding the term “coma” is true?

A. All conditions that cause coma result in irreversible brain damage.
B. Catatonia is a form of coma.
C. Coma can be used synonymously with the term persistent vegetative state.
D. Coma is defined as a sleeplike state with eyes closed from which the patient cannot be aroused.
E. Coma refers to a large group of disorders that lead to impaired consciousness.

V-85. Intraparenchymal intracranial pressure monitoring is preferred over ventriculostomy in which of the following patients?

A. A 24-year-old man admitted with traumatic brain injury following a motor vehicle accident and a Glasgow Coma Scale score of 6.
B. A 35-year-old woman with autoimmune hepatitis admitted with fulminant hepatic failure and an international normalized ratio of 3.5.
C. A 48-year-old man admitted to the intensive care unit with subarachnoid hemorrhage following a rupture of an anterior cerebral artery aneurysm.
D. A 68-year-old woman admitted with a hemorrhagic stroke in the right temporal region with associated midline shift visualized on CT scan.
E. All of the above are appropriate candidates for ventriculostomy.

V-86. A 55-year-old woman is admitted to the ICU following a subarachnoid hemorrhage caused by a rupture of the posterior communicating artery. The patient is treated with intravascular placement of a coil in the aneurysm, and a ventriculostomy is placed for intracranial pressure (ICP) monitoring. On arrival to the intensive care unit after surgery, she is intubated and minimally responsive to painful stimuli. She does not respond to voice. The initial ICP is 45 mmHg, and the initial blood pressure is 138/85 (mean arterial pressure, 103 mmHg) with the head of the bed elevated at 30 degrees. The ICP remains at 45 mmHg over the next 5 minutes. What would you recommend next in the management of this patient?

A. Administer 30 mL of 23.4% hypertonic saline.
B. Administer dexamethasone 4 mg every 6 hours.
C. Do nothing as patient has an adequate cerebral perfusion pressure.
D. Drain ventriculostomy to attain an ICP <20–25 mmHg.
E. Increase respiratory rate on the ventilator to decrease the $PaCO_2$ to 30 mmHg.

V-87. A 56-year-old man is admitted to the hospital following a witnessed cardiac arrest. On arrival of emergency medical personnel, the rhythm is ventricular fibrillation. The patient is cardioverted into a sinus rhythm with return of spontaneous circulation. His estimated duration without circulation is 10 minutes. Electrocardiogram demonstrated evidence of acute myocardial infarction in an anterior distribution. The patient is treated with primary angioplasty of a 100% occlusion of the proximal left anterior descending artery. He is brought to the intensive care unit intubated and requires use of norepinephrine to maintain his mean arterial pressure at greater than 60 mmHg. Initial neurologic examination shows absence of corneal and gag reflexes. When you move the head side to side, the eyes move in concert with the head movement and do not stay fixed. Intermittent myoclonus is present. You are considering the use of hypothermia. Which of the following statements correctly characterizes the use of hypothermia in this patient?

A. A head CT should be performed to determine the extent of cerebral edema before deciding on whether to employ therapeutic hypothermia.
B. Temperature management should be directed at prevention of fevers only with a target temperature of 36°C (96.8°F).
C. Therapeutic hypothermia is recommended to target a temperature of 32–34°C (89.6–93.2°F) for 24 hours.
D. There is no role for therapeutic hypothermia because the patient’s prognosis is very poor.
E. There is no role for therapeutic hypothermia because it does not change patient outcomes.

V-88. Which of the following statements regarding cerebral perfusion and autoregulation is true?

A. Cerebral autoregulation is mediated by medium to large vessels and can be seen during cerebral angiography.
B. Cerebral blood flow is directly proportional to perfusion pressure at all times.
C. Cerebral perfusion pressure is defined as the mean systemic arterial pressure minus the intracranial pressure (ICP).
D. Hypocapnia and alkalosis cause cerebral vasodilation leading to increased cerebral blood flow and an elevation in intracranial pressure.
E. Permissive hypercapnia is an effective way to lower ICP.

V-89. A 47-year-old man with a history of chronic alcohol use is brought to the emergency room by his fiancé for altered mental status and difficulty ambulating. His initial chemistry panel is notable for a sodium level of 129 mEq/L, a serum osmolality of 260 mOsm/L, and a glucose of 55 g/dL. On examination, he is confused and only able to respond to simple commands. He has difficulty with lateral gaze in both directions as well as an ataxic gait. He also has a length-dependent sensory neuropathy to his mid-shins bilaterally. Which of the following is likely true about his current presentation?

A. Administration of IV dextrose will most likely lead to a rapid improvement in his current condition.
B. Exocytotoxic damage from the accumulation of glutamate is partly to blame for his current syndrome.
C. He probably has osmotic demyelination syndrome from a recent rapid drop in his serum sodium level.
D. Most of his symptoms can be attributed to the direct toxic effects of alcohol.
E. The lateral gaze difficulty suggests that he has had bilateral infarctions of his 8th nerve nuclei.

V-90. A 58-year-old male with hypertension and diabetes is 3 years out from a living-related kidney transplant. He is brought to the emergency department by his nephew after a witnessed seizure and loss of vision. Prior to the episode he had been feeling relatively well, without any fever or chills, although he did complain of a headache over the last 24 hours. He has been compliant on his immunosuppressive regimen, which includes tacrolimus and low-dose prednisone. He has baseline hypertension with his last clinic blood pressures recorded in the 150s–170s systolic. His allograft function has been stable. On physical examination his pulse is 85 beats/min, blood pressure is 160/90, respiratory rate is 20 beats/min, and oxygen saturation 96% on room air. On neurologic examination he is tired appearing and slow to respond to questions. He is unable to see even bright lights with either eye. He is still complaining of a headache. Initial laboratory testing reveals a normal chemistry panel and normal white blood cell count. His tacrolimus level is 8 ng/mL. He undergoes emergent MRI with axial fluid-attenuated inversion recovery, which is shown in Figure V-90. Which of the following is the likely etiology of his symptoms?

A. His current syndrome is likely the result of endothelial damage related to calcineurin inhibitor use.
B. His elevated blood pressure has likely caused a disruption in the blood-brain barrier leading to cerebral edema, headaches, and seizures.
C. He has acute tacrolimus toxicity.
D. He has had a large posterior circulation stroke.
E. He most likely has progressive multifocal leukoencephalopathy from JC virus related to his chronic immunosuppression.

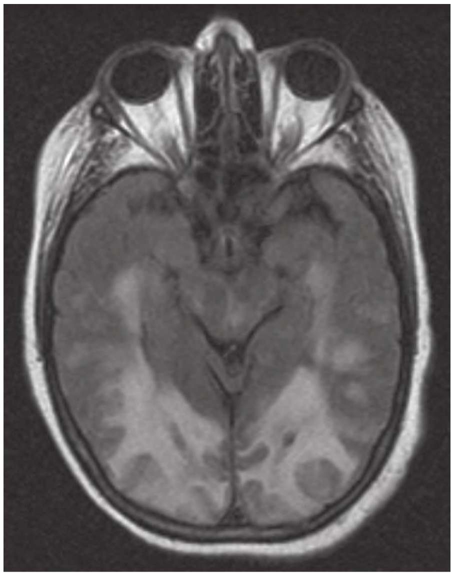


FIGURE V-90

V-91. A 67-year-old previously healthy female is admitted to the hospital with 2 days of fever, cough, and shortness of breath. She is found to have *Legionella* pneumonia and requires intubation and mechanical ventilation for evolving acute respiratory distress syndrome (ARDS). In addition to low tidal volume ventilation, she requires high levels of positive end-expiratory pressure (PEEP) and FiO_2. She is eventually placed in the prone position and undergoes 3 days of neuromuscular blockade to try to optimize her respiratory mechanics and oxygenation. After failing to improve over 7 days, she is administered high-dose methylprednisolone in an attempt to combat the fibroproliferative phase of ARDS. She ultimately undergoes tracheostomy. Beginning on the 12th day of her hospital course, her oxygenation slowly improves and she is weaned to an FiO_2 of 0.40 and PEEP of 5. However, she is unable to tolerate pressure support ventilation or tracheostomy trials due to a rapid respiratory rate and small tidal volumes. On neurologic examination she is noted to have profound weakness in her shoulders, biceps, triceps, hip flexors, and knee extensors/flexors. She is able to move her wrists and hands, as well as her ankles. Her reflexes are intact throughout. Her sensory examination is limited by intermittent delirium, which makes it hard to interpret the findings. Which of the following is the most likely explanation for her weakness and failure to wean from mechanical ventilation?

A. Critical illness polyneuropathy
B. Guillain-Barré syndrome
C. Myasthenia gravis
D. Prolonged action of neuromuscular blockade
E. Thick-filament myopathy

V-92. A 56-year-old woman is admitted to the intensive care unit (ICU) with a thunderclap headache and a rupture of an aneurysm of the anterior cerebral artery. She is treated with endovascular coiling. On admission to the ICU, she was originally intubated and sedated. Over the course of 4 days, she is extubated but continues to demonstrate right hemiparesis and aphasia. Seven days after her presentation, she abruptly declines with alert mental status and marked worsening of her hemiparesis. A head CT is performed urgently and does not show any progression of bleeding or widening of the ventricles. She has been on nimodipine 60 mg every 4 hours since presentation. What is the most likely diagnosis for her worsened condition?

A. Cerebral edema
B. Hydrocephalus
C. Hyponatremia
D. Rerupture of the coiled aneurysm
E. Vasospasm

V-93. What treatment would you recommend for the patient in questions V-92 at this time?

A. Consult neurosurgery for clipping of the aneurysm
B. Free water restriction
C. Placement of a ventriculostomy
D. Intubation with hyperventilation and treatment with mannitol
E. IV norepinephrine and consultation for percutaneous transluminal angioplasty

V-94. A 48-year-old female is admitted to the neurological intensive care unit with a subarachnoid hemorrhage from a previously unknown saccular aneurysm of his middle cerebral artery. He is treated with endovascular coiling and requires ventriculostomy for intracranial pressure monitoring because of altered mental status. He is on nimodipine for prevention of cerebral vasospasm. He is slowly improving, but on hospital day 6 he is noted to have worsening confusion. His laboratory data at the time are notable for a serum sodium of 125 mEq/dL. Which of the following is most likely true about his hyponatremia?

A. He likely has hypervolemic hyponatremia that can be treated with normal saline infusion.
B. His hyponatremia is likely caused by a natriuresis induced by nimodipine.
C. His hyponatremia should be treated with fluid and free water restriction.
D. Permissive hyponatremia is well tolerated in patients with subarachnoid hemorrhage.
E. This is cerebral salt wasting and may require treatment with hypertonic saline.

V-95. A 75-year-old female develops an acute-onset, severe headache while carrying her luggage up a ramp to board a cruise ship. The headache is diffuse and is associated with neck stiffness. She has vomited once. On examination, her temperature is 37.3°C (99.2°F), blood pressure is 145/70, heart rate is 92 beats/min, respiratory rate is 15 breaths/min, and oxygen saturation is 97% while breathing room air. Her neurologic examination does not reveal any focal deficits. Which of the following is likely true about her current headache?

A. A head CT will likely be unrevealing.
B. She probably has meningitis and needs urgent antibiotics, neuroimaging, and a lumbar puncture.
C. The lack of significant hypertension probably means that this is not related to a vascular issue.
D. This is most likely a thunderclap headache and should be managed with analgesics.
E. Xanthochromia on a lumbar puncture would suggest the presence of blood in the cerebrospinal fluid from a subarachnoid hemorrhage.

ANSWERS

V-1. **The answer is B.** *(Chap. 278)* The alveolar-arterial oxygen (A-a O_2) difference can be helpful in distinguishing hypoventilation (elevated PCO_2) as a cause of hypoxemia. The A-a O_2 difference on room air should be less than 15 mmHg in a young adult and typically increases slightly with age. The A-a O_2 difference cannot easily be interpreted when the FiO_2 is greater than 0.21. The A-a O_2 difference on room air is elevated in situations of hypoxemia due to ventilation-perfusion (V/Q) mismatch, shunt, or diffusion defect. It will be normal when the hypoxemia is solely due to hypoventilation. In this case, the gradient is 7.5 mmHg, consistent with hypoventilation secondary to a presumed narcotic overdose. Asthma and pulmonary embolism typically cause hypoxemia due to V/Q mismatch. Pneumococcal and pneumocystis pneumonias cause hypoxemia for multifactorial reasons, including shunt.

V-2. **The answer is A.** *(Chap. 278)* Interstitial lung disease (ILD) is typically characterized by a restrictive ventilatory defect on lung volume testing as the stiffer lungs have a higher elastic recoil pressure. This is defined by a total lung capacity (TLC) less than 80% of predicted. Most patients with a restrictive ventilatory defect due to parenchymal lung disease will have a normal FEV_1/FVC ratio (as in this case) with an FVC that falls in concordance with the TLC. ILD also usually causes a problem with gas transfer and leads to a diffusing capacity for carbon dioxide (DLCO) that is abnormally low. A restrictive ventilatory defect may also be caused by a disorder of the chest wall, such as scoliosis, or by a neuromuscular disease, such as amyotrophic lateral sclerosis. A low TLC coupled with a normal DLCO could indicate chest wall disease or neuromuscular disease as the cause of the restrictive ventilatory defect, as gas transfer would be preserved. A high TLC (hyperinflation) can be seen in severe obstructive lung disease. In the case of asthma, the DLCO will be normal or elevated, but in the case of emphysema, the DLCO will be reduced.

V-3. **The answer is D.** *(Chap. 279)* This patient is presenting with subacute dyspnea, stridor, and airflow obstruction, which are consistent with a diagnosis of subglottic stenosis related to his prior prolonged mechanical ventilation. This is confirmed by the finding of fixed airflow obstruction on the flow-volume loop. Flow-volume loops are derived from spirometry. Following a maximum inspiratory effort from residual volume, an individual forces the maximum volume of air from their lungs, and the resultant flows are plotted against the volume. By convention, inspiration is shown on the lower portion of the curve and expiration is on the top. There are characteristic patterns of airflow obstruction that can be evaluated by examining this curve (Figure V-3B). A fixed central airflow obstruction results in flattening of the flow-volume loop in both inspiration and expiration, yielding the characteristic boxlike effect, as shown in this patient's flow-volume loop. Examples of fixed airflow obstruction include tracheal stenosis and an obstructing central airway tumor. Other patterns of large airway obstruction are a variable intrathoracic obstruction and variable extrathoracic obstruction. In these situations, flattening of the flow-volume curve occurs on only one limb of the flow-volume loop, and the pattern of flattening can be explained by the dynamic changes in pressure that affect the trachea. A variable intrathoracic obstruction causes flattening of the flow-volume curve only on expiration. During inspiration, the pleural pressure is more negative than the tracheal pressure, and the trachea remains unimpeded to flow. However, when pleural pressure rises on expiration relative to tracheal pressure, there is collapse of the trachea and flattening of flow-volume curve. An example of a variable intrathoracic obstruction is tracheomalacia. In contrast, the variable extrathoracic defect leads to flattening of the flow-volume loop on inspiration but not expiration.

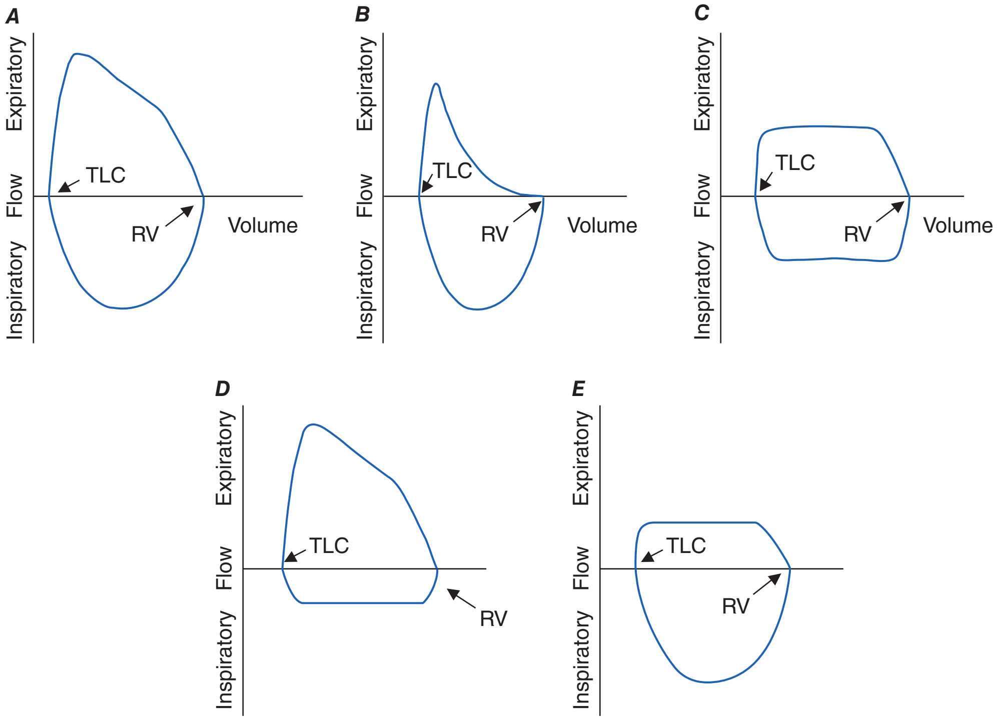


FIGURE V-3B *Abbreviations:* RV, residual volume; TLC, total lung capacity.

The relevant pressure acting on airflow in the trachea in an extrathoracic obstruction is atmospheric pressure. During inspiration, the tracheal pressure drops below atmospheric pressure, leading to compromised airflow and the characteristic flattening of the flow-volume loop. However, tracheal pressure rises above atmospheric pressure during expiration, leading to a normal expiratory curve.

V-4 to V-7. The answers are C, B, D, and A, respectively. *(Chap. 279)* Ventilatory function can be easily measured with lung volume measurement and the FEV_1/FVC ratio. A decreased FEV_1/FVC ratio is characteristic of obstructive lung diseases. Alternatively, low lung volumes, specifically decreased total lung capacity (TLC), and occasionally decreased residual volume (RV) are characteristic of restrictive lung diseases. With extensive air trapping in obstructive lung disease, TLC is often increased, and RV may also be increased. Vital capacity is proportionally decreased. Maximal inspiratory pressure (MIP) measures respiratory muscle strength and is decreased in patients with neuromuscular disease. Thus, myasthenia gravis will produce low lung volumes and decreased MIP, whereas patients with idiopathic pulmonary fibrosis will have normal muscle strength and subsequently a normal MIP but decreased TLC and RV. In some cases of pulmonary parenchymal restrictive lung disease, the increase in elastic recoil results in an increased FEV_1/FVC ratio. The hallmark of obstructive lung disease, such as chronic obstructive pulmonary disease, is a decreased FEV_1/FVC ratio.

V-8. The answer is C. *(Chap. 279)* In this patient presenting with multilobar pneumonia, hypoxemia is present that does not correct with increasing the concentration of inspired oxygen. The inability to overcome hypoxemia or the lack of a notable increase in PaO_2 or SaO_2 with increasing fraction of inspired oxygen physiologically defines a shunt. A shunt occurs when deoxygenated blood is transported to the left heart and systemic circulation without having the capability of becoming oxygenated (right-to-left shunt). Causes of shunt include alveolar collapse (atelectasis), intra-alveolar filling processes, intrapulmonary vascular malformations, or structural cardiac disease leading to right-to-left shunt. In this case, the patient has multilobar pneumonia leading to alveoli that are being perfused but unable to participate in gas exchange because they are filled with pus and inflammatory exudates. Acute respiratory distress syndrome is another common cause of shunt physiology. Ventilation-perfusion mismatch is the most common cause of hypoxemia and results when there are some alveolar units with low ratios (low ventilation to perfusion) that fail to fully oxygenate perfused blood. When blood is returned to the left heart, the poorly oxygenated blood admixes with blood from normal alveolar units. The resultant hypoxemia is less severe than with shunt and can be corrected by increasing the inspired oxygen concentration. Hypoventilation with or without other causes of hypoxemia is not present in this case, as the $PaCO_2$ <40 mmHg indicates hyperventilation. The acidosis present in this case is of a metabolic rather than a respiratory source. Because the patient is paralyzed, she is unable to increase her respiratory rate above the set rate of the ventilator to compensate for the metabolic acidosis.

V-9. The answer is A. *(Chap. 279)* Functional residual capacity (FRC) refers to the volume of air that remains in the lung at end expiration following a normal tidal respiration. This volume of air represents the point at which the outward recoil of the chest wall is in equilibrium with the inward elastic recoil of the lungs. In emphysema, the elastic recoil of the lungs is reduced (lung compliance is higher), so the FRC will be higher. All of the other conditions will either reduce the outward recoil of the chest wall (abdominal muscle paralysis, diaphragmatic weakness, and obesity), or increase the elastic recoil of the lungs (pulmonary fibrosis), which would lead to a reduction in the FRC.

V-10. The answer is E. *(Chap. 279)* This patient with asthma presents with hypoxemia and a reduced $PaCO_2$. A low $PaCO_2$ rules out hypoventilation as the cause of her initial hypoxia. Increased dead space alone would not affect oxygenation and would be expected to result in an increased $PaCO_2$ if alveolar ventilation was not increased to compensate. After being placed on oxygen, the PaO_2 increases notably, which argues against shunt physiology since a shunt does not substantially correct with supplemental oxygen. Asthma is characterized by airways hyper-reactivity that leads to areas of ventilation-perfusion mismatch. Hypoxemia results from areas of low ventilation with normal to high perfusion. This can be easily corrected with supplemental oxygen. Asthma does not reduce the surface area for gas exchange in the lung. In fact, during periods of hyperinflation as might occur in asthma, the diffusing capacity may be increased.

V-11. **The answer is C.** *(Chap. 280)* This patient presents with a slowly progressive illness manifested by dyspnea on exertion, dry cough, clubbing, and the presence of crackles on examination. In addition, the pulmonary function tests demonstrate restrictive ventilatory defect and a diffusion defect. This scenario is characteristic of an individual with interstitial lung disease (ILD), most commonly idiopathic pulmonary fibrosis in individuals at this age. A more thorough history should be obtained to determine whether there are any other exposures or symptoms that could identify other causes of ILD, such as hypersensitivity pneumonitis or collagen vascular–associated lung disease. The next step in the evaluation of this patient is to perform a high-resolution CT scan (HRCT) of the chest. HRCT employs thinner cross-sectional images at approximately 1–2 mm rather than the usual 7–10 mm. This creates more visible details and is particularly useful for recognizing subtle changes of the interstitium and small airways including ILD, bronchiolitis, and bronchiectasis. Bronchoscopy with transbronchial biopsy typically does not provide the detail required to adequately diagnose ILD. It may be considered if there are specific features on HRCT that would suggest an alternative diagnosis or there is suspicion of hypersensitivity. However, in most instances, the pathologic diagnosis of ILD requires a surgical lung biopsy to provide definitive diagnosis. This patient's symptoms do not suggest coronary artery disease or congestive heart failure. Thus, echocardiography and nuclear stress testing are not indicated. At this point, there is no indication for a positron emission tomography scan looking for malignancy or inflammation.

V-12. **The answer is A.** *(Chap. 280)* This patient likely has sarcoidosis involving her airways, lung parenchyma, and lymph nodes. Bronchoscopy with transbronchial biopsy and endobronchial ultrasound-guided transbronchial needle aspiration of her hilar nodes would be the least invasive and most effective way to make the histopathologic diagnosis of sarcoid. Unlike many types of interstitial lung disease, the noncaseating granulomas of sarcoidosis are fairly easy to diagnose from the small samples of transbronchial biopsy or core lymph node biopsy. Sarcoid rarely involves the pleura so pleuroscopy and pleural biopsy would be unlikely to yield the diagnosis. Mediastinoscopy can be an effective way to sample mediastinal lymph nodes, but it is not a good approach to sample hilar lymphadenopathy. In this case it is also more invasive than bronchoscopy. Transthoracic needle biopsy is not an appropriate sampling technique for interstitial lung disease. Video-assisted thoracoscopic surgery would be likely to provide the diagnosis in this case, but it would also be more invasive than bronchoscopy.

V-13. **The answer is E.** *(Chap. 281)* The patient in this clinical scenario presents with symptoms typical of asthma, including shortness of breath and episodic wheezing. She also manifests evidence of atopy, the most common risk factor for developing asthma, with sensitivity to outdoor allergens and cats. In addition, the patient has a history of allergic rhinitis and eczema, both of which are commonly seen in individuals with asthma. Indeed, over 80% of asthma patients have a concomitant diagnosis of allergic rhinitis. Atopy is present in 40–50% of the population of affluent countries, but only a small proportion of these individuals develop asthma. Many studies have shown a genetic predisposition via family history and recent genome-wide screens, but no single genetic profile has shown high positive predictive value. Overall, the prevalence of asthma in developed countries has increased over the last 30 years, but recently it has leveled off, with a prevalence of about 15% in children and 10–12% in adults. Asthma deaths remain rare and have decreased in recent decades. In the 1960s, asthma deaths did increase with an overuse of short-acting β-agonist medications. However, since the introduction of inhaled corticosteroids as maintenance therapy, deaths have declined. Risk factors for fatal asthma include frequent use of rescue inhalers, lack of therapy with inhaled corticosteroids, and prior hospitalizations for asthma. Interestingly, the overall disease severity does not vary significantly within a given patient over the course of the disease. Individuals who have mild asthma typically continue to have mild asthma, whereas those with severe disease present with severe disease. Diagnosis of asthma can be made by demonstrating airflow obstruction with significant reversibility on bronchodilator administration. In this case, the FEV_1/FVC ratio is decreased to 70%, which is low. In addition, the FEV_1 increases by 12.4% and 230 mL. This meets the criteria for bronchodilator reversibility of increases of at least 200 mL and 12%. Bronchoprovocation testing with methacholine can be considered in individuals who have suspected asthma but have normal pulmonary function tests.

V-14. **The answer is B.** *(Chap. 281)* The pathology of asthma has largely been determined by examining bronchial biopsies of patients with asthma as well as the lungs of individuals who die from asthma. These pathologic changes are centered around the airways with sparing of the alveolar spaces. The airways are infiltrated by eosinophils, activated T lymphocytes, and activated mucosal mast cells. However, the degree of inflammation does not correlate with the severity of asthma. Another common finding in all asthmatics and individuals with eosinophilic bronchitis is thickening of the basement membrane due to collagen deposition in the subepithelium. The airway smooth muscle is hypertrophied as well. Overall, this leads to thickening of the airway wall, which may also exhibit edematous fluid, particularly in those with fatal asthma. In cases of fatal asthma, it is also common to find multiple airways that are occluded by mucus plugs. However, the disease is limited to the airways, and infiltration of the alveolar spaces by inflammatory cells is not seen.

V-15. **The answer is C.** *(Chap. 281)* The preferred method for diagnosing asthma is demonstration of airflow obstruction on spirometry that is at least partially reversible. This is demonstrated in option C, with a decreased FEV_1/FVC ratio, decreased FEV_1, and a significant increase in FEV_1 following administration of albuterol. For an individual to be considered responsive to a bronchodilator, the individual should experience an increase in either FEV_1 or FVC of at least 200 mL and 12%, respectively. Option A describes someone with postviral cough syndrome, which can persist for several weeks following a viral upper respiratory infection. Option B describes someone with exercise-induced bronchoconstriction (EIB), which, in the absence of other symptoms to suggest asthma, should not be diagnosed as asthma. Isolated EIB lacks the characteristic airway inflammation of asthma and does not progress to asthma. Although it is estimated that 80–90% of individuals with asthma experience EIB, many individuals who have EIB do not also have asthma. EIB is caused by hyperventilation with inhalation of cool dry air that leads to bronchospasm. Option D describes someone with occupational asthma that has occurred after working with animals in the medical laboratory for many years. Symptoms that are characteristic of occupational asthma are symptoms only while at work that improve on the weekends and during holidays. Option E describes someone with chronic obstructive pulmonary disease (COPD). In COPD, 25–48% of individuals can demonstrate bronchial hyperresponsiveness in response to inhalation of methacholine.

V-16. **The answer is B.** *(Chap. 281)* Although not all individuals with atopy will develop asthma, atopy is the single most important risk factor for developing asthma. Air pollution, particularly indoor air pollution from biomass fuels and cigarette smoking, and pollution from traffic have been shown to be important risk factors for asthma development. The incidence of asthma is rising in developing countries, likely caused by increased urbanization. While viral infections can be important triggers for asthma exacerbations, there is some controversy as to whether or not early viral infections predispose to asthma development. Vitamin D deficiency has been associated with asthma prevalence, but there is no clear evidence that it is causative.

V-17. **The answer is E.** *(Chap. 281)* This patient with mild intermittent asthma and seasonal allergies has required increased use of her short-acting β-agonist to control her symptoms. She would be a good candidate for an inhaled corticosteroid (ICS) as part of a step-up approach to her management. Persistent eosinophilia despite maximal doses of an inhaled corticosteroid might be an indication for therapy with an IL-5 inhibitor, but this patient has not yet received an ICS and has fairly minor symptoms. Similarly, an elevated IgE level despite ICS therapy might indicate either the need for IgE-specific therapy or prompt a search for allergic bronchopulmonary aspergillosis. Her symptoms do not yet rise to that level of investigation at this point in time. It would not be necessary to perform a full set of pulmonary function tests, although it might be helpful to document her current peak expiratory flow rate or FEV_1 to objectively measure the severity of her airflow obstruction. A leukotriene antagonist is usually reserved for patients who have persistent symptoms despite treatment with both ICS and a long-acting β-agonist.

V-18. **The answer is C.** *(Chap. 282)* Acute eosinophilic pneumonia is an acute respiratory syndrome that often presents with a clinical picture that is difficult to differentiate from other forms of acute lung injury or acute respiratory distress syndrome (ARDS). Clinically, patients present with a prodrome of fevers, malaise, myalgias, night sweats, dyspnea, cough, and pleuritic chest pain. Physical examination may demonstrate high fevers, bibasilar rales, and rhonchi. The clinical course is frequently marked by rapid clinical progression to hypoxemic respiratory failure that requires mechanical ventilation. Chest radiography typically shows bilateral pulmonary infiltrates. This clinical picture clearly overlaps with infectious causes of respiratory failure and ARDS. However, the hallmark of acute eosinophilic pneumonia is the finding of >25% eosinophils in the bronchoalveolar lavage (BAL) fluid. Acute eosinophilic pneumonia most frequently presents in individuals between the ages of 20 and 40 years and is more common in men. There is no epidemiologic link between the diagnosis and a prior history of asthma. However, several case reports have linked development of acute eosinophilic pneumonia to recent initiation of cigarette smoking or exposure to other environmental stimuli, including dust. A BAL showing eosinophilia >25% is sufficient to establish the diagnosis of acute eosinophilic pneumonia. A surgical lung biopsy is not necessary. If performed, it would demonstrate eosinophilic infiltration with acute and organizing diffuse alveolar damage. Peripheral eosinophilia is not present acutely at disease onset, but it often becomes present between days 7 and 30. Other organ failure is typically not present initially. The disease has a high degree of corticosteroid responsiveness and a good prognosis. Initiation of therapy with corticosteroids should not be delayed. Although there is no recommended dose of steroids for therapy, patients are often initiated on therapy with IV glucocorticoids with rapid improvement in hypoxemic respiratory failure. The expected clinical course is complete resolution of clinical and radiographic features of the disease over several weeks without relapse on tapering of steroids.

V-19 and V-20. **The answers are B and E, respectively.** *(Chap. 282)* The patient has a subacute presentation of hypersensitivity pneumonitis related to exposure to bird droppings and feathers at work. Hypersensitivity pneumonitis is a delayed-type hypersensitivity reaction that has a variety of presentations. Some people develop acute onset of shortness of breath, fevers, chills, and dyspnea within 6–8 hours of antigen exposure. Others may present subacutely with worsening dyspnea on exertion and dry cough over weeks to months. Chronic hypersensitivity pneumonitis presents with more severe and persistent symptoms along with clubbing. Progressive worsening is common with the development of chronic hypoxemia, pulmonary hypertension, interstitial pulmonary fibrosis, and respiratory failure. The diagnosis relies on a variety of tests. Peripheral eosinophilia is not a feature of this disease as the disease is mediated through T-cell inflammation. Other nonspecific markers of inflammation may be elevated, including the erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, and serum immunoglobulins. Neutrophilia and lymphopenia can be seen. If a specific antigen is suspected, serum precipitins directed toward that antigen may be demonstrated. However, these tests are neither sensitive nor specific for the presence of disease. Chest radiography may be normal or show a diffuse reticulonodular infiltrate. Chest CT is the imaging modality of choice and shows ground-glass infiltrates in the lower lobes. Centrilobular infiltrates are often seen as well. In the chronic stages, patchy emphysema is the most common finding. Histopathologically, interstitial alveolar infiltrates predominate, with a variety of lymphocytes, plasma cells, and occasionally eosinophils and neutrophils seen. Loose, noncaseating granulomas are typical. Treatment requires removing the individual from exposure to the antigen. If this is not possible, the patient should wear a mask that prevents small-particle inhalation during exposure. In patients with mild disease, removal from antigen exposure alone may be sufficient to treat the disease. More severe symptoms require therapy with glucocorticoids at an equivalent prednisone dose of 1 mg/kg daily for 7–14 days. The steroids are then gradually tapered over 2–6 weeks.

V-21. **The answer is E.** *(Chap. 282)* Allergic bronchopulmonary aspergillosis (ABPA) is common in patients with cystic fibrosis (CF) and can be a cause of recurrent exacerbations and worsening respiratory symptoms. Patients may present with a markedly elevated serum IgE level that would warrant more extensive investigations including skin testing for *Aspergillus* reactivity, serum precipitins for *Aspergillus* and *Aspergillus*-specific IgG and IgE. Bronchoalveolar lavage is rarely indicated in patients with CF as they often make copious amounts of secretions that can be sent for culture. This patient's presentation and radiographic appearance are not suggestive of acute pulmonary embolism. Elevated levels of expired nitric oxide can be a marker of an asthma flare of CF flare but is rarely used in clinical practice outside of a clinical trial.

V-22. **The answer is E.** *(Chap. 282)* This patient likely has an acute vasculitis-associated mononeuritis of the peroneal nerve from previously undiagnosed eosinophilic granulomatosis with polyangiitis (EGPA). This diagnosis was previously called the Churg-Strauss syndrome. Her weight loss and fevers could have been the early symptoms of her evolving clinical syndrome. Oftentimes, patients with EGPA will have poorly controlled asthma-like symptoms prompting treatment with corticosteroids. The steroids can mask the other manifestations of vasculitis. There is no evidence of acute trauma, and no history of chronic leg crossing to suggest a mechanical injury to the common peroneal nerve. Acute stroke can cause foot drop but it would be rare for this to be the only manifestation of a cortical infarct. She will require therapy with glucocorticoids plus likely additional disease-modifying medication(s) such as cyclophosphamide or mepolizumab.

V-23. **The answer is C.** *(Chap. 283)* Mesothelioma is a rare malignancy of the pleura and peritoneum, with almost all cases associated with asbestos exposure. It is notable that the exposure to asbestos could seem almost minimal but still confer significant risk. Exposures of less than 1–2 years that occurred more than 40 years in the past have been demonstrated to confer increased risk of mesothelioma. Although tobacco smoking in association with asbestos exposure increases the risk of lung cancer severalfold, there is no additive or exponential risk of mesothelioma in those who smoke. Mesothelioma most often presents with a persistent unilateral pleural effusion that may mask the underlying pleural tumor. However, the pleura may be diffusely thickened. Typically, large pleural effusions would cause expansion of the hemithorax with mediastinal shift away from the side of the pleural effusion. However, even with large effusions, no mediastinal shift is seen on chest radiograph in patients with mesothelioma because the pleural thickening associated with the disease leads to a fixed chest cavity size and thoracic restriction. The most difficult diagnostic dilemma in these patients is to differentiate mesothelioma from metastatic lung carcinoma (usually adenocarcinoma) as many patients are at risk for both tumors, and lung cancer is by far the most common malignancy seen in individuals with asbestos exposure and cigarette smoking. Pleural fluid cytology is not adequate for the diagnosis of most individuals with mesothelioma, with positive samples for the disease in less than 50% of individuals. Most often, video-assisted thoracoscopy is required to directly visualize the pleural and direct biopsy sampling. Unfortunately, there is no proven effective therapy for mesothelioma, and most patients die from local extension of the disease.

V-24. **The answer is D.** *(Chap. 283)* The patient presents with acute-onset pulmonary symptoms, including wheezing, with no other medical problems. He is a farmer and was recently handling hay. The clinical presentation and radiograph are consistent with farmer's lung, hypersensitivity pneumonitis caused by *Actinomyce*s. In this disorder, moldy hay with spores of actinomycetes are inhaled and produce hypersensitivity pneumonitis. The disorder is seen most commonly in rainy periods when the spores multiply. Patients present generally 4 to 8 hours after exposure with fever, cough, and shortness of breath without wheezing. Chest radiographs often show patchy bilateral upper lobe infiltrates. The exposure history will differentiate this disorder from other types of pneumonia.

V-25. **The answer is E.** *(Chap. 283)* Work in an electronics factory could mean that she has been exposed to beryllium and has developed chronic beryllium disease (CBD). Beryllium exposure can cause an acute pneumonitis with diffuse alveolar infiltrates but more commonly causes a chronic granulomatous disease that can look similar clinically and pathologically like sarcoidosis. Steel workers in the past were commonly exposed to asbestos. The fibers could be carried home on clothing and lead to potential exposure in household contacts. Asbestos exposure can lead to interstitial lung disease, chronic pleural disease, mesothelioma, or lung cancer (particularly in smokers). Exposure to nitrogen dioxide in grain silos can cause acute pneumonitis or lead to obliterative bronchiolitis. Exposure to grain dust can also lead to chronic obstructive disease. Soldering can lead to exposure from a number of different toxic exposures such as cadmium, which can cause obstructive disease. Textile workers are at risk of developing byssinosis from exposure to cotton dust. This manifests as an asthma-like syndrome that is worse at the beginning of the work week.

V-26. **The answer is D.** *(Chap. 283)* This patient presents with an occupational history and radiograph typical for silicosis. Patients with silicosis are at increased risk of certain types of infection because the silica particles impair macrophage function. As a result, patients with latent tuberculosis (TB) and silicosis should be treated for longer than other patients to make sure that the infection is effectively eradicated. Silica exposure does not cause a positive purified protein derivative (PPD). Invasive aspergillosis is more common in patients with silicosis but would not be expected to cause a positive PPD. A biopsy would not be needed to exclude active pulmonary TB. Sputum smear and culture would likely be sufficient in this case. A biopsy would also not be needed to make a presumptive diagnosis of silicosis based on the radiographic appearance and history.

V-27. **The answer is D.** *(Chap. 284)* Bronchiectasis is a common disorder that refers to an irreversible dilation of the airways that affects the lung in a focal or diffuse pattern. Historically, bronchiectasis has been characterized pathologically as cylindrical, varicose, or cystic in nature. There are numerous causes of bronchiectasis including infectious, inherited, immunologic, and idiopathic causes. The most common cause of bronchiectasis worldwide is postinfectious following tuberculosis infection. However, in developed countries, other causes are more common. The most common cause in developed countries is cystic fibrosis (CF); CF patients develop clinically significant bronchiectasis in late adolescence or early adulthood. Most children with CF are diagnosed currently through newborn screening programs, which were introduced in all states within the last decade. However, adults may continue to present with milder forms of the disease, so clinicians should continue to have a high degree of clinical suspicion for CF when an individual presents with a new diagnosis of bronchiectasis. Epidemiologically, individuals presenting with CF bronchiectasis will typically be younger than individuals with non-CF bronchiectasis. In contrast, non-CF bronchiectasis more commonly affects non-smoking women older than 50 years. The clinical presentation of bronchiectasis is a daily cough productive of thick tenacious sputum. Physical examination demonstrates both crackles and wheezing on examination. In CF, the disease findings are more predominant in the upper lobes, whereas in certain other causes (chronic aspiration, immunoglobulin deficiency), there is a lower lobe predominance. Clubbing is variably present and generally only seen in more advanced disease. The diagnosis of bronchiectasis is determined by the presence of the disease on a chest CT imaging. Chest radiography is not sensitive for the diagnosis of bronchiectasis, particularly early in the disease process. It may show “tram tracks” indicating dilated airway. Chest CT is the diagnostic modality of choice for confirming the diagnosis. Findings include demonstration of dilated, nontapering airways that may be filled with mucus. In addition, signet-ring signs may also be seen where the airway is greater than 1.5 times the size of the adjacent blood vessel. Other findings include bronchial wall thickening, inspissated secretion with a “tree-in-bud” pattern, and cysts emanating from the bronchial wall. Once bronchiectasis has been confirmed on CT imaging, other tests may be indicated in this patient to determine the etiology of bronchiectasis. Testing should be guided by the history and physical examination and may include sputum culture for mycobacteria and fungal organisms, immunoglobulin levels, autoimmune panel, sweat chloride testing, nasal nitric oxide testing (for primary ciliary dyskinesia), bronchoscopy, and/or tests of swallow function. Despite thorough evaluation, in as many as 25–50% of individuals referred for workup of bronchiectasis, no specific cause is ever identified.

V-28. **The answer is C.** *(Chap. 284)* This patient likely has rheumatoid arthritis (RA) with secondary Sjögren syndrome. Both RA and Sjögren syndrome can lead to airway inflammation and bronchitis. In RA, it can often be difficult to determine whether the bronchiectasis is from the disease itself, or perhaps from prior therapies that can be toxic to the airway (e.g., gold, penicillamine, etc.). Cystic fibrosis (CF) can present later in life, but this patient's joint disease and fatigue suggest a possible collagen vascular disease that should be investigated before CF-specific testing should be considered. Nasal mucosal biopsy to look for ciliary dysfunction is likewise probably premature at this point. Sputum cultures should be obtained to look for atypical mycobacterial infection as well as bacterial pathogens to inform future antibiotic decisions and to decide if suppressive therapy is warranted. Tuberculosis can cause bronchiectasis but is less common in the United States. Sweat chloride testing is helpful in making the diagnosis of CF, but again it would not be the first test to send off in this patient with a possible autoimmune disease.

V-29. **The answer is E.** *(Chap. 285 and J Pediatrics 181: S4, 2017)* Cystic fibrosis (CF) is a common autosomal recessive disorder that affects 1 of every 3300 live births in the Caucasian population of North America and Europe. There have been more than 2000 mutations identified in the gene for the cystic fibrosis transmembrane conductance regulator (CFTR) protein—the abnormal protein identified in CF. This protein is a large transmembrane protein involved in the transport of chloride and other ions, and abnormalities of the CFTR lead to abnormalities of salt and water transport. The primary clinical manifestations of CF are due to the effects of the mutated CFTR in the lungs, gastrointestinal tract, and pancreas. In the lungs, abnormal CFTR leads to thick, sticky mucus with abnormal mucociliary clearance. A patient will have recurrent respiratory infections with development of cystic bronchiectasis over time. The presenting manifestation in infancy is often meconium ileus and can lead to constipation and distal intestinal obstruction in adults. Failure of CFTR in the pancreas prevents appropriate release of pancreatic enzymes to allow for proper digestion of food, especially fatty foods, with resultant malnutrition and steatorrhea. While most patients with CF present in infancy or childhood, about 5% of all individuals with CF will not be diagnosed until adulthood. Presenting symptoms in adulthood can be myriad and often result from minor mutations of the *CFTR* gene. These symptoms can include recurrent lung and sinus infections, malnutrition, sinus disease, and infertility, especially absence of the vas deferens in men. The standard test for the diagnosis of CF is the sweat chloride test. Elevated values are pathognomonic for CF, with a cutoff of >60 mmol/L in adults being diagnostic. Values greater than 40 mmol/L fall within the indeterminate range. Given the large number of mutations that can cause CF, genetic testing can be expensive and is not the first test performed when CF is suspected. A screening CF genetic panel often only identifies between approximately 20 and 80 of the common CF mutations. If only one mutation is identified, then this may represent the carrier state, or it could represent CF with a rarer mutation requiring more detailed genetic analysis, including full gene sequencing. In such cases, referral to a tertiary CF care center is helpful for data interpretation. In some instances, nasal potential difference testing can be helpful because CF patients demonstrate an elevated baseline nasal potential difference with failure to respond to stimulation with β-agonists. Presence of *Pseudomonas aeruginosa* in sputum is common in adults with CF, but it is not specific for the diagnosis of the disease because bronchiectasis from any cause can lead to *P. aeruginosa* colonization.

V-30. **The answer is B.** *(Chap. 285)* This patient most likely is experiencing a flare of his cystic fibrosis (CF) related to chronic *Pseudomonas* infection. The most appropriate treatment would be dual therapy with two IV antipseudomonal agents. Inhaled antibiotics can be an effective therapy to suppress chronic colonization with *Pseudomonas* but would be unlikely to be effective as monotherapy during an acute exacerbation. Methicillin-resistant *Staphylococcus aureus* (MRSA) can be a pathogen in CF, and vancomycin might be a reasonable empiric antibiotic during a flare in a patient with known prior MRSA colonization, but it should be paired with antipseudomonal agents. Atypical mycobacterial infections are increasing in frequency in patients with CF, but empiric therapy in a flare should not be directed toward atypical mycobacteria in the absence of a positive culture. Allergic bronchopulmonary aspergillosis (ABPA) is more common in CF patients, and should be pursued as a diagnostic possibility in patients who do not respond to treatment with IV antibiotics directed against *Pseudomonas*. Testing for ABPA including an IgE level, precipitins to *Aspergillus*, and *Aspergillus*-specific IgG and IgE should be undertaken before initiation of treatment with steroids and antifungal agents.

V-31. **The answer is A.** *(Chap. 285)* Lack of functional cystic fibrosis transmembrane conductance regulator (CFTR) at the apical plasma membrane of epithelial cells leads to a depleted pericellular fluid layer, which in turn leads to ciliary dysfunction and failure to clear mucus. CFTR is situated in the apical plasma membranes of acinar and other epithelial cells where it regulates the amount and composition of secretion by exocrine glands. In numerous epithelia, chloride and bicarbonate release is followed passively by the flow of water, allowing for mobilization and clearance of exocrine products.

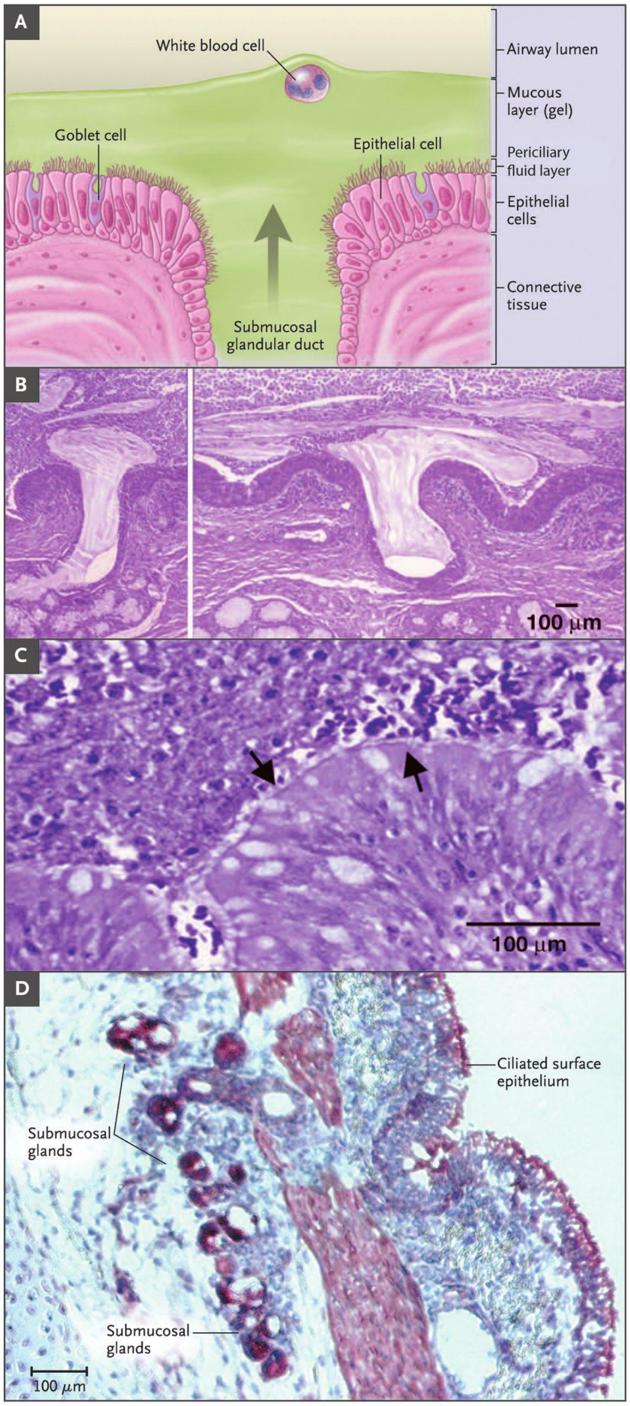

A
White blood cell
Airway lumen
Mucous layer (gel)
Goblet cell
Epithelial cell
Periciliary fluid layer
Epithelial cells
Connective tissue
Submucosal glandular duct
B
100 μm
C
100 μm
D
Ciliated surface epithelium
Submucosal glands
Submucosal glands
100 μm

FIGURE V-31 Reproduced with permission from Rowe SM, Miller S, Sorscher EJ: Cystic fibrosis. *N Engl J Med* 352:1992, 2005.

Along respiratory mucosa, CFTR is necessary to provide sufficient depth of the periciliary fluid layer (PCL), allowing normal ciliary extension and mucociliary transport (Figure V-31). CFTR-deficient airway cells exhibit depleted PCL, causing ciliary collapse and failure to clear overlying mucus. In airway submucosal glands, CFTR is highly expressed in acini and may participate both in the formation of mucus and extrusion of glandular secretion onto the airway surface. The failure to clear thick, inspissated secretions leads to an aggressive, unrelenting, neutrophilic inflammatory response with release of proteases and oxidants leading to airway remodeling and bronchiectasis. This further predisposes to recurrent infection.

V-32. **The answer is D.** *(Chap. 286)* Acute exacerbations of chronic obstructive pulmonary disease (COPD) are a frequent cause of morbidity and mortality in COPD, contributing to >70% of health care expenditures for COPD. Risk factors for the development of acute exacerbation include severity of airflow obstruction (FEV_1 <50% predicted), history of prior exacerbations, and elevated ratio of pulmonary artery to aorta on chest CT. Acute exacerbations of COPD cost over $10 billion to the health care system in the United States annually. Thus, determining the causes of exacerbations and prevention of future exacerbations have been important targets in the care of COPD patients. Most acute exacerbations are associated with airway inflammation or infection, including acquiring a new strain of bacteria or a viral respiratory infection. Therefore, strategies for prevention have been primarily focused on decreasing inflammatory responses and preventing infections. The selective phosphodiesterase-4 inhibitor roflumilast has been demonstrated to decrease exacerbation frequency in individuals with COPD who have symptoms of chronic bronchitis and frequent exacerbations. However, it has limited effects of pulmonary function and chronic respiratory symptoms. The macrolide antibiotic azithromycin has both anti-inflammatory and antibiotic properties. In a randomized controlled trial, it has been shown to decrease exacerbation frequency and increase the time to first exacerbation when administered at a dose of 500 mg daily, not 250 mg three times weekly. Other interventions that also decrease exacerbation frequency include use of inhaled glucocorticoids in individuals with frequent exacerbations or asthmatic symptoms and influenza vaccination. Long-acting anticholinergic medications and long-acting β-agonists decrease exacerbations as well. Oxygen therapy and nocturnal ventilation are not indicated for prevention of exacerbations. Theophylline yields mode improvements in lung function but has no proven effect on exacerbations.

V-33. **The answer is E.** *(Chap. 286)* Acute exacerbations of chronic obstructive pulmonary disease (COPD) are marked by an increase in dyspnea, an increase in sputum, and a change in sputum color. Acute exacerbations of COPD account for substantial health care expenditures annually in the United States, with significant morbidity and mortality associated with these exacerbations. Prompt treatment can improve symptoms and decrease hospitalizations and mortality in this setting. In patients presenting with hypercarbic respiratory failure in the setting of an acute exacerbation, the treatment that has demonstrated the strongest reduction in mortality, when compared with traditional mechanical ventilation, is noninvasive positive-pressure ventilation (NIPPV). NIPPV also decreases the need for endotracheal intubation, complications, and length of stay in the hospital. Antibiotics, bronchodilators, and glucocorticoids are all cornerstones of therapy in the treatment of acute exacerbations in COPD but have not been demonstrated in clinical trials to have similar mortality benefits in the situation of acute hypercarbic respiratory failure. Specifically, no benefit is demonstrated for IV versus oral corticosteroids. Likewise, the choice of antibiotic should be made based on local susceptibility patterns, and the need for broad-spectrum antibiotics that cover for *Pseudomonas* spp. is not typically indicated. Recent studies have demonstrated that high-flow nasal oxygen may be an effective alternative to NIPPV, with improved outcomes (need for mechanical ventilation) and improved patient comfort.

V-34. **The answer is C.** *(Chap. 286)* The only therapies that have been proven to improve survival in patients with chronic obstructive pulmonary disease (COPD) are smoking cessation, oxygen in patients with resting hypoxemia, and lung volume reduction surgery in a very small subset of highly selected patients. This patient probably has resting hypoxemia resulting from the presence of an elevated jugular venous pulse, pedal edema, and elevated hematocrit. Theophylline has been shown to increase exercise tolerance in patients with COPD through a mechanism other than bronchodilation. Oral glucocorticoids are not indicated in the absence of an acute exacerbation and may lead to complications if they are used indiscriminately. Atenolol and enalapril have no specific role in therapy for COPD but are often used when there is concomitant hypertension or cardiovascular disease.

V-35. **The answer is E.** *(Chap. 286)* The single greatest risk to this man's health is his continued smoking. An emerging body of evidence demonstrates that combining pharmacotherapy with traditional supportive approaches considerably enhances the chances of successful smoking cessation. He has Global Initiative for Chronic Obstructive Lung Disease stage 2 disease and has stable symptoms without evidence of recurrent exacerbations. There is no indication to add an additional long-acting bronchodilator to his current long-acting muscarinic antagonist regimen. Inhaled corticosteroids can be effective in reducing exacerbation rates but carry a risk of increased pneumonia and would not be indicated in someone without frequent exacerbations. Treatment of hypoxemia is important to prevent long-term complications such as cor pulmonale, but hypoxemia is rare in patients with only mild lung function impairment. Pulmonary rehabilitation has been shown to improve symptoms and reduce hospitalization rates in patients with chronic obstructive pulmonary disease, but this gentleman regularly exercises and is without significant symptoms currently. Focusing on smoking cessation would be more important in the short term.

V-36. **The answer is D.** *(Chap. 286)* This patient presents with early-onset emphysema. Although this could be entirely due to his cigarette smoking, the early onset and radiographic appearance should raise a concern for alpha-1 antitrypsin (α1AT) deficiency. About 1% of chronic obstructive pulmonary disease (COPD) patients have evidence of α1AT deficiency. Many variants of the protease inhibitor (PI or SERPINA1) locus that encodes α1AT have been described. The common M allele is associated with normal α1AT levels. The S allele, associated with slightly reduced α1AT levels, and the Z allele, associated with markedly reduced α1AT levels, also occur with frequencies of >1% in most white populations. Rare individuals inherit null alleles, which lead to the absence of any α1AT production through a heterogeneous collection of mutations. Individuals with two Z alleles or one Z allele and one null allele are referred to as PiZ, which is the most common form of severe α1AT deficiency. He likely has the PiZ phenotype (i.e., he has two abnormal alleles) given the early onset and severity of his obstructive disease. While environmental pollutants are an increasing cause of COPD worldwide, this is more common in developing countries in which women and children are exposed to smoke from biomass fuels during indoor cooking. The absence of bronchiectasis or other clinical features makes cystic fibrosis unlikely. Atypical mycobacterial infection can be a cause of cough and sputum production but usually does not cause isolated panacinar emphysema on imaging. Bronchiectasis and bronchiolitis would be a more common radiographic manifestation of atypical mycobacteria infection. Acute pulmonary embolism should be considered in all patients who present with a COPD exacerbation. Chronic thromboembolic disease would more likely present with air trapping and mosaic perfusion on CT imaging.

V-37 and V-38. **The answers are E and C, respectively.** *(Chap. 287)* Idiopathic pulmonary fibrosis (IPF) is the most common cause of idiopathic interstitial pneumonia. The disease typically presents with progressive dyspnea on exertion and dry cough in an older individual. IPF is rare in individuals younger than age 50 years. On physical examination, inspiratory crackles and clubbing are common. Pulmonary function tests demonstrate restrictive ventilatory defect (low total lung capacity, low residual volume, low vital capacity) with a low diffusing capacity for carbon dioxide. As in the chest CT shown (see Figure V-37), there is typically interstitial fibrosis that is worse in the bases and begins in the subpleural areas, often associated with traction bronchiectasis and honeycombing. Atypical findings that should cause one to consider an alternative diagnosis include the presence of ground-glass infiltrates, nodular opacities, an upper lobe predominance of disease, and prominent hilar or mediastinal lymphadenopathy. Bronchoscopic biopsy is insufficient for histologic confirmation, and surgical lung biopsy is required for definitive diagnosis, although in a patient with a typical presentation and chest CT surgical intervention may not be indicated. The histologic hallmark of IPF is usual interstitial pneumonia, but it can also occur in rheumatologic diseases or due to secondary exposures. In these cases, the prognosis is better than when the diagnosis is IPF. If no other secondary cause is identified, the diagnosis of IPF is given. The natural history of IPF is one of continued progression of disease and a high mortality rate. Acute exacerbations also occur with a rapid progression of symptoms associated with a pattern of diffuse ground-glass opacities on CT. These are associated with a high mortality. Until recently, no treatment had been demonstrated to slow progression of disease. Historically, IPF was felt to be refractory to medical therapy with lung transplantation the only viable therapeutic option. This dogma changed in 2014 with large clinical trials that demonstrated that antifibrotic therapy (pirfenidone and nintedanib) can slow decline of lung function in IPF patients. Further meta-analyses have suggested that antifibrotic therapy may also improve survival. In contrast, treatment with immunosuppression, which had been commonly prescribed to many IPF patients, has now been demonstrated (in some cases) to be associated with increased morbidity and mortality. Nintedanib is an intracellular tyrosine kinase inhibitor that inhibits several growth factors including vascular endothelial growth factor, fibroblast growth factor, and platelet-derived growth factor. Pirfenidone is an oral antifibrotic medication that has been demonstrated to decrease fibroblast proliferation and collagen synthesis. Therapies that have been shown to not benefit patients with IPF include glucocorticoids, immunosuppressive agents, and *N*-acetylcysteine.

V-39. The answer is D. *(Chap. 287)* This patient is presenting with subacute pulmonary symptoms, intermittent fevers, myalgias, and malaise. The biopsy shows a pattern of cryptogenic organizing pneumonia (COP). COP (formerly bronchiolitis obliterans organizing pneumonia) usually presents in the fifth or sixth decades with a flulike illness. Symptoms include fever, malaise, weight loss, cough, and dyspnea. Inspiratory crackles are common, and late inspiratory squeaks may also be heard. Pulmonary function testing reveals a restrictive defect. The typical pattern on chest CT is patchy areas of airspace consolidation, nodular opacities, and ground-glass opacities that occur more frequently in the lower lung zones. Pathology shows the presence of granulation tissue plugging airways, alveolar ducts, and alveoli. There is frequently chronic inflammation in the alveolar interstitium. Treatment with high-dose steroids is effective in two-thirds of individuals, with most individuals able to be tapered to lower doses over the first year. Azathioprine is an immunosuppressive therapy that may be considered in COP unresponsive to glucocorticoids; it would not be a first-line agent used without concomitant steroid therapy. Because most patients with COP respond to corticosteroids, referral for lung transplantation is not required unless there is a failure to respond to therapy. Nintedanib and pirfenidone are treatments for idiopathic pulmonary fibrosis.

V-40. The answer is C. *(Chap. 287)* This patient most likely has nonspecific interstitial pneumonia in the context of a collagen vascular disease. Her young age at onset, Raynaud syndrome, muscle aches, and mechanic's hands suggest the possibility of an anti-synthetase syndrome, in which Jo-1 is the most commonly described autoantibody. Interstitial lung disease can be the first manifestation of a collagen vascular disease or can occur in the presence of other systemic signs and symptoms. If characteristic autoantibodies and other systemic features are present, a lung biopsy is not needed to make the diagnosis, and it can carry with it significant risk. video-assisted thoracoscopic surgery/surgical biopsy has a much higher diagnostic yield than bronchoscopic biopsy, although diagnoses such as sarcoidosis, eosinophilic pneumonia, and hypersensitivity pneumonitis can often be made with transbronchial biopsy. The CT findings and history in this case are not consistent with hypersensitivity pneumonitis, so a workup for antibody response to environmental antigens is unlikely to be helpful.

V-41. The answer is E. *(Chap. 287)* This patient likely has either respiratory bronchiolitis-interstitial lung disease (RB-ILD), or perhaps eosinophilic granuloma (EG). Both of these disorders are directly tied to smoking, and smoking cessation is oftentimes the only treatment required to reverse the inflammatory process. Azathioprine has been used to treat a number of inflammatory lung diseases, but would not be effective in RB-ILD or EG. Nintedanib is an antifibrotic that has been shown to slow down the progression of idiopathic pulmonary fibrosis. Although nintedanib is currently being studied in a number of different ILDs, it has not yet shown to be effective in other disorders. Prednisone might have some positive impact in patients with RB-ILD, but this is usually reserved for patients whose disease progresses despite smoking cessation, or if the disease is rapidly progressing. Sirolimus has been used to treat lymphangioleiomyomatosis, but this disease is exceedingly uncommon in males.

V-42. **The answer is C.** *(Chap. 288)* Empyema refers to the presence of a grossly purulent pleural effusion, which is present in this clinical scenario. The management of an empyema requires drainage of the infected pleural space, typically via placement of a chest tube. A randomized, placebo-controlled clinical trial demonstrated improved outcomes with use of both alteplase (tissue plasminogen activator) and deoxyribonuclease (DNase) twice daily for 3 days beginning within the first day after chest tube placement. The trial was conducted using a factorial design comparing the combination therapy to placebo and to either therapy alone. The combination of alteplase and DNase showed improved resolution of pleural fluid, shorter duration of hospital stay, and less need for surgical intervention when compared with placebo or either therapy alone (Rahman NM et al: *N Engl J Med* 365:518–526, 2011).

V-43. **The answer is C.** *(Chap. 288)* Tension pneumothorax is a life-threatening complication that must be rapidly recognized and alleviated. If undetected, it will rapidly progress to cardiovascular collapse and death. Tension pneumothorax most commonly occurs during mechanical ventilation and during resuscitative efforts. An initial sign during mechanical ventilation is high peak inspiratory pressures or difficulty with ventilation. Hypotension and hypoxemia are signs of impending cardiovascular collapse and are caused by decreased venous return to the heart and reduced cardiac output. The physical examination may show absence of breath sounds on the affected side with enlargement of the hemithorax, hyperresonance to percussion, and mediastinal shift to the contralateral side. A chest radiograph would be confirmatory, but in the acute setting, there may not be time to obtain the testing. If clinical suspicion is high, treatment should not be delayed as tension pneumothorax is a medical emergency and the patient is likely to die if the tension is not relieved. A large-bore needle should be placed into the pleural space through the second anterior intercostal space. If a large amount of air escapes after the needle is inserted, the diagnosis is confirmed. The needle should remain in place until definitive treatment with a tube thoracostomy can be performed.

V-44. **The answer is B.** *(Chap. 288)* A primary spontaneous pneumothorax occurs in the absence of trauma to the thorax. Most individuals who present with a primary spontaneous pneumothorax are young, and primary spontaneous pneumothorax occurs almost exclusively in cigarette smokers, the primary risk factor. Primary spontaneous pneumothorax is also more common in men and has been associated with a tall, thin body habitus. The primary cause is the rupture of small apical pleural blebs or cysts, and the CT scan of the chest is often normal. About half of individuals will experience more than one primary spontaneous pneumothorax. The initial treatment is simple needle aspiration, which is most commonly done with ultrasound or CT guidance. Oxygen is given simultaneously to speed resorption of the residual air in the pleural space. If conservative treatment fails, tube thoracostomy can be performed. Pneumothoraces that fail to resolve or are recurrent often require thoracoscopy with stapling of blebs and pleural abrasion, a treatment that is effective in almost 100% of cases.

V-45. **The answer is A.** *(Chap. 288)* This patient likely has bilateral effusions from congestive heart failure. The effusion on the right is classified as an exudate by Light criteria. Although Light criteria almost never misclassify an exudative effusion as a transudate, about 25% of transudates may be misclassified as an exudate. This patient's presentation, including improvement with furosemide, suggests that his effusions are from congestive heart failure. The administration of diuretics might increase the likelihood of a transudative effusion from heart failure misclassified as an exudate. The serum protein to fluid protein gradient greater than 3 mg/dL in this case argues that this effusion most likely is a transudate; the difference between serum and pleural fluid protein would typically be less in an exudative process. One could make the argument that the effusion did not need to be sampled in the first place if the patient was clinically improving with management of heart failure. There is no need for more aggressive diagnostic or therapeutic procedures for a heart failure–related pleural effusion if the patient is improving clinically.

V-46. **The answer is B.** *(Chap. 288)* Viral infection may account for as many as 20% of unexplained pleural effusions, which may be exudative as in this case. Since this patient with an unexplained exudative effusion and no evidence of empyema is improving clinically, no further workup is indicated at this time other than close follow-up to make sure that his symptoms and the effusion do not recur. Pulmonary embolism is a common cause for exudative pleural effusions. However, the viral prodrome in this case, the lack of clear risk factors for pulmonary embolism, and his clinical improvement argue against the need to perform a CT angiogram or additional diagnostic tests.

V-47. **The answer is B.** *(Chap. 289)* Chronic fibrosing mediastinitis most commonly occurs after granulomatous inflammation in mediastinal lymph nodes that leads to an exuberant calcification response. Over time, the inflammation can cause significant disruption to the vital structures that course through the mediastinum and lead to the clinical symptoms of fibrosing mediastinitis. The most common causes of fibrosing mediastinitis are histoplasmosis and tuberculosis. Other causes include sarcoidosis, silicosis, or other fungal diseases. Symptoms are related to compression of mediastinal structures including the superior vena cava, pulmonary arteries or veins, or large airway compression. The phrenic or recurrent laryngeal nerves may also become paralyzed. The most common symptom is dyspnea on exertion. Patients may also develop chronic cough with lithoptysis or hemoptysis due to erosion of the calcified lymph nodes into airways. Patients may describe lithoptysis as gritty or sandy sputum. Hemoptysis can be large volume and may necessitate surgical intervention for control. However, other than antituberculous therapy for tuberculous mediastinitis, no medical or surgical therapy has any effectiveness on the treatment of fibrosing mediastinitis. This patient most likely has histoplasmosis as the cause of her disease because histoplasmosis is endemic in Indiana. Because the fibrosing mediastinitis is a sequela of an old infection, the urine *Histoplasma* antigen test would not yield a positive result.

V-48. **The answer is E.** *(Chap. 290)* Obesity hypoventilation syndrome (OHS) is a disorder of chronic hypoventilation that has an unknown prevalence as no large population studies have been conducted. However, the prevalence is expected to increase as the prevalence of obesity is rising worldwide. OHS requires a body mass index >30 kg/m^2 and the presence of chronic alveolar hypoventilation for diagnosis, with a daytime awake $PaCO_2$ ≥45 mmHg. In more than 90% of cases, concomitant obstructive sleep apnea (OSA) is also present. The pathogenesis of OHS is not fully understood, although it is known that there is a downregulation of the central respiratory drive in response to carbon dioxide. Multiple physiologic factors acting together likely lead to this including OSA, increased work of breathing, respiratory muscle impairment, ventilation-perfusion mismatching, and depressed central chemo-responsiveness to hypoxemia and hypercarbia. Most patients present with daytime sleepiness, headaches, signs of volume overload, and symptoms typical of OSA. These patients should be treated with weight loss and positive airway pressure therapy (PAP). Sustained weight loss will lead to improvements in $PaCO_2$ over time. Continuous PAP (CPAP) therapy does lead to improvement in daytime hypercapnia and hypoxemia in more than half of patients with OHS and OSA but is not recommended for use if patients have sustained hypoxemia after resolution of obstructive apneic events. In these individuals bilevel PAP (BiPAP) therapy is used. BiPAP is also used if a patient cannot tolerate the typically high levels of CPAP required for treatment. Some patients with OHS may present acutely with decompensated symptoms of right heart failure and respiratory failure as in this scenario. When a patient presents in acute decompensated

OHS, BiPAP is the treatment of choice acutely as well. Even in patients who have previously failed home noninvasive therapy, this remains the treatment of choice for their acute condition and may prevent intubation and mechanical ventilation. The *PHOX2b* gene mutation plays no role in OHS but is associated with congenital central hypoventilation syndromes.

V-49. The answer is E. *(Chap. 290)* Patients with amyotrophic lateral sclerosis (ALS) often develop hypoventilation due to the involvement and weakness of their inspiratory respiratory muscles (e.g., diaphragm, intercostal muscles, sternocleidomastoids). Noninvasive positive pressure ventilation (NIPPV) has been used successfully in the therapy of patients with hypoventilation such as ALS. Nocturnal NIPPV can improve daytime hypercapnia, prolong survival, and improve health-related quality of life. Current ALS guidelines are to institute NIPPV if symptoms of hypoventilation exist and $PaCO_2$ is ≥45 mmHg, nocturnal desaturation to <89% is documented for 5 consecutive minutes, maximal inspiratory pressure is <60 cmH_2O, or FVC is <50% predicted. Symptoms of hypoventilation are not particular to ALS and may include the following: dyspnea during activities of daily living, orthopnea in diseases that affect diaphragm function, poor-quality sleep, daytime hypersomnolence, early morning headaches, anxiety, and impaired cough in neuromuscular disease.

V-50. The answer is C. *(Chap. 290)* This patient has an acute on chronic respiratory acidosis with a chronic compensatory metabolic alkalosis. Her pH is reduced and her $PaCO_2$ is elevated, which confirms the presence of a respiratory acidosis. In the acute setting, every rise in $PaCO_2$ of 10 mmHg leads to a drop in pH of 0.08. If this were all acute, her expected pH would be about 7.12. Since her pH is only 7.30, and her serum bicarbonate is elevated, she must have a chronic respiratory acidosis with renal metabolic compensation, most likely on the basis of her severe COPD. The normal kidneys will respond to the chronic respiratory acidosis by retaining bicarbonate in an attempt to correct serum pH; therefore her current acidosis is acute on chronic.

V-51. The answer is B. *(Chap. 291)* Obstructive sleep apnea/hypopnea syndrome (OSAHS) is a common condition estimated to affect up to 2–15% of middle-aged individuals and >20% of elderly individuals. It is associated with repeated collapse of the upper airway during sleep leading to repeated arousals and fragmented sleep. This patient exhibits multiple risk factors and gives a strong history to support a diagnosis of OSAHS, placing him at high risk to have moderate to severe OSAHS. The greatest risk factor the patient has that places him at high risk for disease is obesity. Approximately 40–60% of cases of OSAHS are attributable to excess body weight. The second major risk factor for OSAHS is male sex because men are two to four times more likely to have OSAHS than women. The reasons men develop OSAHS more frequently include greater central obesity and relatively longer pharyngeal length, which in turn contribute to greater upper airway collapsibility. In addition, female sex hormones provide a stabilizing effect on the upper airway and stimulate ventilatory drive. Thus, premenopausal women are relatively protected from OSAHS at comparable levels of obesity when compared with men. Other risk factors that this patient has include a positive family history of the disease and hypertension. Other common risk factors for OSAHS in the general population include craniofacial abnormalities, adenotonsillar hypertrophy, various endocrine syndromes (acromegaly, hypothyroidism), increasing age, and some ethnic groups. For instance, individuals of Asian descent often develop OSAHS at a lower range of body mass index, most likely due to ethnic differences in craniofacial structure. In addition, individuals of African American race are at higher risk of OSAHS when compared with whites. This patient also gives many symptoms that are concerning for OSAHS including loud snoring, witnessed apneas, and daytime sleepiness. Given that there is a high clinical suspicion of disease, home sleep testing will likely be adequate for diagnosis of disease in this patient. Home sleep tests can be performed in a variety of ways, but most will record respiratory effort, nasal flow, and oxygen saturation. In a patient with a high suspicion of disease, these tests can be a cost-efficient means of diagnosis. However, the home tests may yield false-negative results because these tests do not measure the electroencephalogram; thus, no accurate measure of sleep time is obtained. Therefore, the respiratory events are determined based on total recording time rather than total sleep time. If a patient is awake during much of the recording time, this could cause a false-negative result. Attended in-lab polysomnography remains the gold standard for diagnosis OSAHS but is significantly more expensive. In this individual with a high pretest suspicion of disease, the cost would not be justified. An overnight oximetry provides only oxygen levels and heart rate and is not adequate for diagnosis of OSAHS. Treatment with a CPAP device may be recommended after a diagnosis is confirmed, but this would not be the next step in the treatment of the patient. The patient has only minimally enlarged tonsils. A tonsillectomy would not be expected to alleviate his symptoms.

V-52. **The answer is E.** *(Chap. 291)* This sleep pattern demonstrates Cheyne-Stokes respiration, a pattern of periodic breathing in which intervals of hyperpnea alternate with intervals of apnea. Respiration waxes and wanes in a crescendo-decrescendo pattern. Cheyne-Stokes respiration is a type of central sleep apnea often associated with heart failure or other low cardiac output states. Pathophysiologically, this occurs because the baseline carbon dioxide during wakefulness is below the apneic threshold during sleep. Thus, at sleep onset, a central apneic event occurs allowing carbon dioxide to rise. When this rise in carbon dioxide is detected centrally, there is an exaggerated respiratory response that leads to hyperpnea and hyperventilation, driving the carbon dioxide levels below the apneic threshold again, creating a self-perpetuating cycle of apnea and hyperpnea. It occurs more commonly in individuals with heart failure or atrial fibrillation due to a delay in circulation time. This prolonged circulation delay between the pulmonary capillaries and the central carbon dioxide–sensing chemoreceptors contributes to these ongoing cycles of hyperpnea and apnea. In many individuals with Cheyne-Stokes respiration, it has been observed that the pattern of breathing may worsen over the course of the night and the fluid is redistributed centrally, further prolonging circulation time. Optimization of volume status or rhythm may improve the disordered nocturnal respiration.

V-53. **The answer is B.** *(Chap. 291)* Oral appliances can be effective in reducing the apnea-hypopnea index (AHI), in some cases by more than 50%, and they have been best studied in patients with mild disease. They work by advancing the mandible, thus opening the airway by repositioning the lower jaw and pulling the tongue forward. They could be considered in this patient with mild disease (AHI <15). Bariatric surgery can be effective in patients with morbid obesity and severe disease but would not be indicated in this patient with a body mass index just above 30 and mild disease. Supplementary oxygen might be effective in decreasing central apneas but is not effective in decreasing obstructive apneas. Upper airway neurostimulation requires further study before it can be routinely recommended. Upper airway surgery such as uvulopalatopharyngoplasty is not as effective as oral airway appliances and is most commonly used in patients with significant snoring.

V-54. **The answer is D.** *(Chap. 292)* Common indications for lung transplantation include chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, cystic fibrosis (CF), emphysema, and pulmonary arterial hypertension (Table V-54A). Five-year survival is similar for all indications for lung transplantation at approximately 50%. For most indications, double lung transplantation is the preferred procedure, and it is mandatory for patients with suppurative lung disease like CF (Table V-54B). In patients with idiopathic pulmonary arterial hypertension, double lung transplantation is preferred because of improved survival and the concern of over circulation in the low-resistance vascular bed transplanted lung when a native lung is present with markedly elevated pulmonary vascular resistance. It is rare for the primary disease to recur after transplantation, and this has not been described in idiopathic pulmonary arterial hypertension. The right ventricle is highly plastic and will generally recover function after elevated pulmonary vascular resistance is removed by lung transplantation. Therefore, it is rare to perform heart-lung transplantation in pulmonary arterial hypertension patients unless there is concomitant complex congenital heart disease that cannot be repaired at the time of lung transplantation.

TABLE V-54A Disease-Specific Guidelines for Referral and Transplantation

Chronic Obstructive Pulmonary Disease
Referral for evaluation • Progressive despite medications, oxygen, and pulmonary rehabilitation FEV$_1$ <25% PaO$_2$ <60 mmHg or PaCO$_2$ >50 mmHg BODE index 5–6 Listing for transplantation • BODE index ≥7 FEV$_1$ <15–20% Moderate to severe pulmonary hypertension Three or more severe exacerbations in preceding year One severe exacerbation with acute hypercapnic respiratory failure
Cystic Fibrosis/Bronchiectasis
Referral for evaluation • FEV$_1$ <30% or rapidly declining despite optimal therapy Pulmonary hypertension (in absence of hypoxemic exacerbation) 6-min walk distance <400 m Clinical deterioration with increasing frequency of exacerbations, with • An episode of acute respiratory failure requiring ventilatory support Increasing antibiotic resistance and poor recovery from exacerbations Worsening nutritional status despite adequate supplementation Refractory or recurrent pneumothorax Life-threatening hemoptysis despite bronchial artery embolization Listing for transplantation • Chronic hypoxemic or hypercapnic respiratory failure Pulmonary hypertension Rapid decline in lung function Long-term noninvasive ventilator support Frequent hospitalization WHO functional class IV
Idiopathic Pulmonary Fibrosis
Referral for evaluation • Pathologic or radiographic evidence of UIP or NSIP regardless of lung function FVC <80% or DLCO <40% Dyspnea or functional limitation attributable to lung disease Any oxygen requirement (rest or exercise) Listing for transplantation • Decrement in FVC ≥10% or in DLCO >15% during 6 months of follow-up Pulmonary hypertension Desaturation to SpO$_2$ <88% during 6-min walk test 6-min walk test distance <250 m or decrement >50 m over 6 months Hospitalization for acute exacerbation
Idiopathic Pulmonary Arterial Hypertension
Referral for evaluation • NYHA functional class III or IV during escalating therapy Use of parenteral therapy regardless of NYHA functional class Rapidly progressive disease Listing for transplantation • NYHA functional class III or IV despite combination therapy with a prostanoid Cardiac index <2 L/min/m^2 or right atrial pressure >15 mmHg 6-minute walk test distance <350 m Progressive right heart failure or significant pericardial effusion or hemoptysis

Abbreviations: BODE, body-mass index (B), airflow obstruction (O), dyspnea (D), exercise capacity (E); FVC, forced vital capacity; FEV$_1$, forced expiratory volume in 1 s; DLCO, diffusing capacity for carbon monoxide; NSIP, nonspecific interstitial pneumonitis; NYHA, New York Heart Association; PaCO$_2$ and PaO$_2$, partial pressures of carbon dioxide and oxygen, respectively, in arterial blood; SpO$_2$, arterial oxygen saturation by pulse oximetry; UIP, usual interstitial pneumonitis; WHO, World Health Organization.
Source: Summarized from Weill D et al: *J Heart Lung Transplant* 34:1, 2015. For BODE index, Celli BR et al: *N Engl J Med* 350:1005, 2004.

TABLE V-54B Recipient Survival, by Pretransplantation Diagnosis

	Survival Rate (%)					
Diagnosis; Transplant Type	3 Months	1 Year	3 Years	5 Years	10 Years	15 Years
Chronic obstructive pulmonary disease[a]						
• Bilateral	93	86	71	59	37	16
• Single	92	84	66	51	24	6
Alpha-1 antitrypsin deficiency emphysema						
• Bilateral	89	81	69	61	40	24
• Single	88	78	62	52	29	13
Cystic fibrosis[a]	93	88	76	63	48	27
Idiopathic pulmonary fibrosis[a]						
• Bilateral	89	82	66	55	34	16
• Single	89	79	58	45	21	7
Idiopathic pulmonary arterial hypertension						
• Bilateral	80	74	62	55	40	28
• Single	71	62	52	41	24	15
Sarcoidosis	86	76	62	55	35	22

[a] Survival cohorts: 2009–2015 for 3 months, 1 year, and 3 years; 1999–2008 for 5 years and 10 years; 1990–1998 for 15 years. For other diagnoses, cohort is 1990–2013 for all survival rates.

Source: Data from www.ishlt.org/registries/slides.asp?slides=heartLungRegistry.

V-55. The answer is D. *(Chap. 292)* This patient likely has primary allograft dysfunction (PAD). This is a form of acute lung injury most likely precipitated by insults to the donor lung during harvesting and transplantation. The treatment is supportive care. This patient has severe PAD (defined by a PaO_2/FiO_2 ratio <200) which is a risk factor for chronic allograft dysfunction. Heart failure is also a concern in a postoperative elderly patient, but the normal left ventricular function coupled with the lack of fluid overload on examination make this less likely. Acute infection is possible after transplant but the early time course and lack of other signs or symptoms of infection are somewhat reassuring. Several immunosuppressants, including tacrolimus and sirolimus, can cause a pneumonitis, but the time course is most consistent with primary graft dysfunction. Noncardiogenic pulmonary edema usually occurs around the time of extubation and is often related to laryngospasm, or perhaps to a drug reaction. This patient is too far out from anesthesia for this to be the cause of his current hypoxia. Hyperacute rejection could present with acute hypoxia and bilateral infiltrates and should also be considered in the differential diagnosis.

V-56. The answer is D. *(Chap. 292)* Bronchiolitis obliterans syndrome (BOS) is one of the most common causes of long-term allograft failure and is the classic form of chronic rejection. It is characterized by a progressive obstructive defect on pulmonary function tests (PFTs), oftentimes with air trapping seen on expiratory CT. Risk factors include primary graft dysfunction, acute cellular rejection, humoral rejection and anti-HLA antibodies, viral infections (cytomegalovirus pneumonia; community-acquired respiratory viral infections), airway colonization by *Pseudomonas aeruginosa* or *Aspergillus fumigatus*, and gastroesophageal reflux. BOS can usually be distinguished from restrictive allograft syndrome (RAS) by the presence of airflow obstruction and the absence of clear infiltrates or fibrosis on CT. RAS usually has a restrictive picture on PFTs. Airway stenosis is a common cause of loss in lung function posttransplant and is likely in part caused by a compromised blood flow at the site of an airway anastomosis. Prior infection or airway colonization with organisms such as *Aspergillus* can also predispose to stenotic lesions. In addition to airway colonization, *Aspergillus* can also cause an invasive pneumonia. Lymphocytic infiltrates around arterioles and bronchioles are a sign of acute cellular rejection. In the case of BOS you could potentially see constrictive bronchiolitis, or progressive scarring of small airways, but this is usually best seen on a surgical lung biopsy and not a transbronchial biopsy.

V-57. **The answer is A.** *(Chap. 293)* Several different severity of illness (SOI) scores have been developed for use in critically ill populations. Two of the most common systems are the Acute Physiology and Chronic Health Evaluation (APACHE II) score and the Simplified Acute Physiology (SAPS II) score. SOI scores are primarily useful as tools to assess populations of critically ill individuals, but the scores do not perform well at predicting individual patient outcomes. These scores are used primarily in clinical trials to compare SOI between groups of patients enrolled in trials. These scores are also used by hospital administrations to assess the quality of intensive care unit care over time and also to help determine appropriate nursing and ancillary support staffing levels. No SOI score should be used to direct an individual patient's care, although decision support tools based on SOI scores are being investigated. The APACHE II score is the most commonly used SOI score. This score assigns values based on a variety of demographic, medical history, and clinical values taking the worst value in the first 24 hours after admission. Population mortality ranges based on published values range from <5–10% for scores between 0 and 4 and as high as 80–90% for scores ≥35 points. Updated versions of the APACHE score (APACHE III and IV) have been published. The SAPS II score is more frequently used in Europe. This score is not disease specific, although it does add higher values for AIDS, metastatic cancer, or hematologic malignancy. Both scores are used in a similar manner.

V-58. **The answer is C.** *(Chap. 293)* Oxygen delivery (Q_{O2}) is a function of both cardiac output (CO) and the oxygen content of the blood (Ca_{O2}) and can be expressed by the following equation:

$$Q_{O2} = CO \times (1.39 \times \text{hemoglobin} \times SaO_2) + (0.003 \times PaO_2)$$

From this equation, the effect of PaO_2 on overall oxygen content and delivery is negligible. The PaO_2 reflects the partial pressure of oxygen dissolved in plasma in equilibrium with hemoglobin saturation. Nearly all oxygen delivered to the tissues is bound to hemoglobin. One can improve oxygen delivery by increasing CO, increasing hemoglobin, or improving oxygen saturation.

V-59. **The answer is A.** *(Chap. 293)* Gastrointestinal bleeding can occur from stress ulcers in the stomach that can form after prolonged mechanical ventilation. It would not be expected to be an acute complication of intubation. Positive pressure ventilation can have a number of effects on cardiac filling pressures. Positive intrathoracic pressure can decrease venous return and reduce right ventricular preload. This can cause a reduction in cardiac output and decrease blood pressure. The effects can be more pronounced in patients with pulmonary hypertension as the positive intrathoracic pressure also increased right ventricular afterload. Following intubation there can be a reduction in catecholamines if the patient was in respiratory distress prior to initiation of sedation and mechanical ventilation. Medications like opiates and propofol can decrease cardiac output and blood pressure. Right main-stem intubation could potentially lead to hypoxemia and cause a reduction in blood pressure.

V-60. **The answer is D.** *(Chap. 293)* There are a number of factors that predict failure to wean from mechanical ventilation during a spontaneous breathing trial. Hypoxemia (SpO_2 <90%), pulse >140, respiratory rate >35 breaths/min, and a systolic blood pressure <90 or >180 all have been associated with failure to successfully wean. A respiratory rate to tidal volume ratio of greater than 105 also predicts extubation failure. In general, successful liberation from mechanical ventilation is predicted by the patient taking slow deep breaths during the spontaneous breathing trial.

V-61 and V-62. **The answers are E and A, respectively.** *(Chap. 294)* This patient has evidence of severe acute respiratory distress syndrome (ARDS). The annual incidence of ARDS is 60 cases per 100,000 population. In individuals admitted to the intensive care unit (ICU) with respiratory failure, approximately 20% of these will meet the criteria for ARDS, although it is generally underrecognized in the ICU population. ARDS is a clinical syndrome of severe dyspnea of rapid onset, hypoxemia, and diffuse pulmonary infiltrates that may lead to respiratory failure. There are myriad causes of ARDS, including sepsis, pneumonia, aspiration pneumonitis, trauma, acute pancreatitis, multiple transfusions, and toxic inhalation injury, among others. The most common causes of ARDS are sepsis and pneumonia, which cause about 40–50% of all cases of ARDS. Clinically, ARDS is diagnosed in the presence of acute bilateral pulmonary infiltrates and hypoxemia without evidence of increased left atrial filling pressure. A consensus panel has recently revised the definition of ARDS into three categories of mild, moderate, and severe based on degree of hypoxemia as determined by the ratio of PaO_2 to FiO_2, commonly called the P:F ratio. Mild ARDS is present if PaO_2/FiO_2 is ≤300 mmHg, but >200 mm Hg. Moderate ARDS is diagnosed when PaO_2/FiO_2 is ≤200 mmHg and >100 mmHg. Severe ARDS is diagnosed when PaO_2/FiO_2 is ≤100 mmHg. In this case, the ratio of PaO_2 to FiO_2 is 80 mmHg, placing the patient in the category of severe ARDS. The natural history of ARDS is three stages: exudative, proliferative, and fibrotic. In the early exudative stage of ARDS, there is an acute injury to alveolar capillary endothelial cells and type I pneumocytes. This results in loss of the normal alveolar barrier with subsequent leakage of protein-rich fluid into the alveoli (noncardiogenic pulmonary edema). In the early phase, the inflammatory cell infiltrate is predominantly neutrophils. Pathologically, the finding is described as diffuse alveolar damage. Hyaline membranes and loss of type I pneumocytes are seen. The exudative phase of ARDS lasts for approximately the first 7 days of illness. The second phase of ARDS is the proliferative phase, which begins around day 7 and continues through day 21. Most patients recover during this phase and are able to be liberated from mechanical ventilation. Histologically, early signs of repair can be seen in this phase with shift to a lymphocyte-predominant infiltrate, proliferation of type II pneumocytes, and organization of alveolar edema. Only a few individuals who develop ARDS fail to recover during the proliferative phase and continue into the fibrotic stage of the disease. Given the timing of the presentation, this patient would be expected to be in the exudative phase of ARDS and exhibit diffuse alveolar damage, loss of type I pneumocytes, and hyaline membranes.

V-63. **The answer is B.** *(Chap. 294)* This individual has severe acute respiratory distress syndrome (ARDS) due to trauma, a pulmonary contusion, and possible transfusion-related lung injury. Mechanical ventilation is frequently necessary for individuals suffering from ARDS and has been essential for prolonging life and improving mortality from this disorder. However, appropriate ventilator management is necessary to prevent further morbidity from ventilator-associated lung injury. ARDS is not experienced uniformly across the lung tissue. The dependent portions of the lungs are typically the most affected, while other areas of the lung may be spared. The portions of the lung that are most affected are poorly compliant and are prone to alveolar collapse. Alternatively, the more normal portions of the lungs have better lung compliance. With positive-pressure ventilation, ventilator-associated lung injury may occur as a result of overdistention of the more normal areas of the lung with resultant perpetuation of alveolar damage and capillary leak in these areas. In the poorly compliant areas, respirations initiated by the ventilator can lead to repetitive opening and closure of alveoli, causing further damage in these areas. Because of this, a strategy that employs low tidal volumes to prevent alveolar overdistention and recurrent alveolar collapse is recommended. The ARDS Network conducted a clinical trial that compared low tidal volume ventilation with conventional ventilation and demonstrated improved mortality with the low tidal volume strategy (31% vs 40%). The recommended initial tidal volume setting is 6 mL/kg of ideal body weight. This strategy is recommended in all patients with ARDS, and the improvement in outcomes is not affected by obesity.

V-64. **The answer is E.** *(Chap. 294)* This patient with acute respiratory distress syndrome (ARDS) is appropriately receiving low tidal volume ventilation and as a result has developed a respiratory acidosis. However, she is tolerating this acidosis from a hemodynamic standpoint so there is no reason to treat this permissive hypercapnia. Increasing the tidal volume would increase her plateau pressure and put her at greater risk of ventilator-induced lung injury. Increasing her respiratory rate to 40 would increase the possibility of air trapping with resulting auto-positive end-expiratory pressure (PEEP), and would likely lead to patient-ventilator dyssynchrony. There is no need to increase her FiO_2 as her PaO_2 and saturation are adequate. Increasing PEEP would possibly increase her plateau pressure and would not be indicated because she is already adequately oxygenating. The best thing to do would be to leave her ventilator settings where they are for the time being.

V-65. **The answer is C.** *(Chap. 294)* Early use of neuromuscular blockade in patients with severe acute respiratory distress syndrome (ARDS) was shown to improve survival in a multicenter study. Fluid restriction or a "conservative" fluid approach has been shown to shorten intensive care unit stay and mechanical ventilation time, although there is no effect on mortality. Glucocorticoids have never been shown to improve outcomes in patients in early ARDS, although they are still commonly used in patients thought to be in the later fibroproliferative phase. Low tidal volume ventilation is the single most important treatment for ARDS and has been shown to reduce mortality by almost 10% over conventional mechanical ventilation. Prone positioning has been shown to improve mortality in moderate to severe ARDS, but it requires a team with experience in the potential complications of proning.

V-66. **The answer is C.** *(Chap. 295)* Noninvasive ventilation (NIV) refers to respiratory support that is provided through a tight-fitting face mask or nasal mask. NIV can be administered with bilevel positive expiratory pressure ventilation or pressure support ventilation. Both modes of ventilation provide a higher positive pressure with inspiration and decrease to a lower pressure with expiration to decrease work of breathing and provide assisted ventilation. The major difficulty with using NIV clinically is poor patient tolerance due to the use of a tight-fitting mask and psychological discomfort and anxiety. The primary group of individuals who have benefited from the use of NIV are those with acute exacerbations of chronic obstructive pulmonary disease (COPD). In those with COPD, several randomized trials have shown low failure rates in individuals with pH of 7.25–7.35, along with decreased need for invasive ventilation, decreased length of intensive care unit stay, and decreased mortality in some studies. In those with pH >7.35, NIV confers no benefit over standard therapy. In those with pH <7.25, use of NIV has a higher failure rate that is inversely proportional to the degree of acidosis. Another group of individuals who may benefit from NIV are those with decompensated systolic heart failure with respiratory acidosis. In these individuals, a large clinical trial demonstrated a decreased need for invasive mechanical ventilation. NIV in these individuals decreased both preload and afterload and can provide assistance to the failing heart (Gray A, et al: *N Engl J Med* 359(2):142–151, 2008). A last group for which NIV has shown promise is in individuals immediately after extubation, especially individuals with COPD or hypercapnic respiratory failure. NIV is associated with higher failure rates in individuals with acute hypoxemic respiratory failure and acute respiratory distress syndrome. Invasive mechanical ventilation is the ventilatory method of choice in these individuals, although not strictly contraindicated. Contraindications to mechanical ventilation include absence of spontaneous respirations, cardiac or respiratory arrest, severe encephalopathy, severe gastrointestinal bleed, hemodynamic instability, unstable angina or acute myocardial infarction, facial surgery or trauma, upper airway obstruction, inability to protect the airway, and inability to clear secretions.

V-67 to V-70. **The answers are C, B, A, and D, respectively.** *(Chap. 295)* Mechanical ventilation can be delivered in many different modes, which refers to the manner in which the breaths are triggered, cycled, and delivered. The most common mode of mechanical ventilation is assist control. This mode is volume cycled and flow limited. An inspiratory cycle may be triggered by patient effort or, if there is no patient effort within a specific time, by a timer within the ventilator. Each breath, whether triggered by patient effort or the ventilator, delivers an operator-specified tidal volume. This mode is frequently the initial mode of mechanical ventilation when a patient is intubated as it ensures a known minute ventilation in the absence of respiratory effort. Common difficulties with the use of assist-control ventilation are asynchrony with the ventilator and tachypnea, which can lead to respiratory alkalosis and/or generation of dynamic hyperinflation. This occurs when a patient triggers an inspiratory cycle before a full exhalation occurs. Commonly known as auto-positive end-expiratory pressure, dynamic hyperinflation can lead to decreased venous return and a fall in cardiac output. It may also lead to barotrauma, including pneumothorax and pneumomediastinum. Intermittent mandatory ventilation (IMV) is a mixed mode of ventilation. IMV is primarily a volume-cycled and flow-limited mode of ventilation and is most often delivered in a synchronized mode (SIMV). The ventilator will deliver a mandatory number of breaths at a specified tidal volume. If a patient breathes only at the set respiratory rate, SIMV is essentially the same as assist-control ventilation. When a patient breathes above the set respiratory rate, the spontaneous breaths may be unassisted or assisted with a pressure support mode of ventilation. SIMV was commonly used as a weaning mode of ventilation, but clinical trials have shown that trials of spontaneous breathing lead to a shorter duration of mechanical ventilation and more rapid extubation. Pressure-controlled ventilation (PCV) is time triggered, time cycled, and pressure limited. This mode is often used in individuals who have preexisting barotrauma or for postoperative thoracic surgery patients. It is also used in acute respiratory distress syndrome to limit ventilator-induced lung injury. In PCV, there is no prespecified minimum tidal volume or minute ventilation. Rather, a specified pressure is set during inspiration by the operator, and the tidal volume and inspiratory flow rate are dependent on lung compliance. Pressure support ventilation (PSV) is patient triggered, flow cycled, and pressure limited. PSV requires a patient to spontaneously initiate respiration because no machine-delivered breaths are given. PSV provides graded assistance through application of an inspiratory pressure that augments spontaneous respiration. The pressure support falls to a specified expiratory pressure when the flow falls below a certain rate. PSV is often combined with SIMV to augment the spontaneously generated breaths. PSV also is used in ventilator weaning as it is generally well tolerated.

V-71. **The answer is A.** *(Chap. 295)* Assist-control ventilation with low tidal volumes has been shown to decrease mortality in patients with acute respiratory distress syndrome (ARDS). Extracorporeal membrane oxygenation has been used as salvage therapy for ARDS but there is debate about when it should be initiated prior to a trial of low tidal volume ventilation. Continuous positive airway pressure and pressure support ventilation would not be appropriate in a patient who has just been sedated and paralyzed for intubation since they rely on spontaneous efforts on the part of the patient. Pressure-controlled ventilation is most appropriate in postsurgical patients when there is concern for high shear forces on an anastomotic site or suture line in the airway or chest.

V-72. **The answer is D.** *(Chap. 295)* Spontaneous breathing trials (SBTs) have been determined to be the best way to assess whether a patient has recovered sufficiently from respiratory failure to be extubated. An SBT can be implemented via T-piece, continuous positive airway pressure at low levels of pressure (1–5 cmH_2O), or pressure support ventilation applied to offset the resistance of the endotracheal tube. A patient will undergo an SBT from 30 minutes to 2 hours to determine whether respiration can be maintained to support liberation from mechanical ventilation. It is important to recognize which patients are appropriate to undergo SBT. The following conditions predict patients who are ready for weaning attempts: (1) lung injury is stable or resolving; (2) gas exchange is adequate, with positive end-expiratory pressure generally <8 cmH_2O and FiO_2 <0.50; (3) hemodynamic parameters are stable without need for ongoing vasopressor support; and (4) the patient has spontaneous respiratory activity. Hemodynamic instability is a contraindication to an SBT. While we normally worry more about hypotension and the need for vasopressor therapy, new-onset hypertension could signify an evolving cardiac, renal, neurologic, or other issue that would need to be addressed before an SBT. Concern for upper airway edema would not be a contraindication to an SBT. However, this concern would need to be addressed prior to removing the endotracheal tube if the patient passed the SBT. Acute kidney injury would not be a contraindication to an SBT but might impact the patient's ability to successfully wean from mechanical ventilation if there were resulting metabolic or fluid balance issues.

V-73. **The answer is A.** *(Chap. 296)* Shock is a complex pathophysiologic process that occurs in response to a decline in tissue perfusion. Clinically, shock states manifest with a mean arterial pressure <60 mmHg. This nonspecific term can be caused by many different etiologies including sepsis, hypovolemia, trauma, hypoadrenal states, neurologic causes, and cardiac causes. Shock states result in a decrease in tissue oxygen delivery. In turn, this creates a multifaceted response that can become a self-perpetuating process that leads to further tissue injury. Hypotension disinhibits the vasomotor center, leading to increased adrenergic output and decreased vagal tone. Norepinephrine leads to significant splanchnic and peripheral vasoconstriction in an attempt to maintain cerebral and cardiac blood flow. Other constrictor substances are secreted as well including angiotensin II, vasopressin, endothelin-1, and thromboxane A_2. In addition, there is pressure to maintain intravascular fluid volume through alterations in hydrostatic pressure and osmolarity. However, constriction of arterioles leads to reduction in capillary hydrostatic pressure and the number of capillary beds perfused. This limits the capillary surface area available for perfusion with the resultant increase in vascular oncotic pressure. This in turn leads to a net reabsorption of fluid into the vascular bed. Metabolic changes including glycolysis, lipolysis, and proteolysis further increase interstitial and intravascular volume at the expense of intracellular volume due to their effects on raising extracellular osmolarity. Within the cells, there is rapid depletion of high-energy phosphate stores. This leads to mitochondrial dysfunction with uncoupling of oxidative phosphorylation with accumulation of reactive oxygen species, lactate, and hydrogen ions. The byproducts of anaerobic metabolism can overcome the compensatory vasoconstrictor mechanisms and lead to further hypotension. Extensive proinflammatory pathways are activated in shock and contribute to the development of multiorgan dysfunction and failure. After the initial insult, a counterregulatory process should be initiated to balance the proinflammatory response. In individuals who have an excessive proinflammatory response that cannot be effectively regulated, the inflammatory process may continue unregulated and lead to further organ injury and failure. At the system level, shock affects a variety of endocrine, cardiac, pulmonary, and renal processes, among others. In addition to increases in norepinephrine, the stress associated with shock increases adrenocorticotropic hormone to increase cortisol secretion. Renin is also released in response to adrenergic discharge and decreased renal perfusion. Renin induces the formation of angiotensin I, which is converted to the active angiotensin II, which is a potent vasoconstrictor. Angiotensin II also stimulates the release of aldosterone and vasopressin. The cardiac response to shock is to initially compensate by increasing heart rate. Many causes of shock, however, are associated with depression of myocardial contractility such that stroke volume is decreased for any given filling pressure. The pulmonary response may lead to development of noncardiogenic pulmonary edema, acute respiratory distress syndrome, and decreased lung compliance. Finally, the kidney responds to shock by conserving salt and water.

V-74. **The answer is C.** *(Chap. 296)* Different causes of shock are associated with different physiologic findings throughout the vascular system. Although rarely used in most cases of shock, a pulmonary artery catheter can be used to measure these values. However, it is important to understand pathologically what occurs in the vascular system. The typical measured variables include cardiac output (CO), systemic vascular resistance (SVR), mixed venous oxygen saturation (SvO_2), central venous pressure (CVP), and pulmonary capillary wedge pressure (PCWP). SvO_2 is an indirect measure of cardiac output and typically falls in low CO states with tissue hypoperfusion. This patient is having anaphylaxis and is developing distributive shock. Patients with distributive shock will have an elevated CO but decreased SVR. Filling pressures will usually be decreased as up to 35% of intravascular volume can become extravasated. Patients who have interruption of sympathetic vasomotor input after high cervical cord injury or major head injury may experience neurogenic shock. In neurogenic shock, there is arteriolar dilation and venodilation. The result is a fall in all variables measured (CO, SVR, SvO_2, CVP, and PCWP) (option E). Hypovolemia is the most common cause of shock and occurs due to acute blood loss or significant loss of plasma volume due to extravascular fluid sequestration. Gastrointestinal or renal fluid losses may also lead to hypovolemic shock. In hypovolemic shock, CO is low; SVR is elevated; and SvO_2, CVP, and PCWP are low (option A). Cardiogenic shock (option B) has similarly low CO, elevated SVR, and low SvO_2. However, CVP and PCWP are elevated. Septic shock can be hyperdynamic or hypodynamic. Early in septic shock, the hyperdynamic state predominates and is associated with increased CO, low SVR, and low SvO_2. CVP and PCWP are variable and may be low, normal, or elevated. The hypodynamic state of septic shock is associated with low CO and high SVR with variable effect of CVP, PCWP, and SvO_2. Shock following trauma is most often due to hypovolemia.

However, after intravascular volume is restored, some individuals will continue to experience hypotension due to loss of plasma volume into the interstitium and injured tissues.

V-75. **The answer is A.** *(Chap. 297)* Sepsis and septic shock represent a harmful host response to infection and are contributing factors to more than 200,000 deaths in the United States each year. Over the last 30 years, the incidence of sepsis has risen along with our aging population. Annually, there are more than 750,000 cases of sepsis yearly with an incidence of 3 per 1000 population. Most cases of sepsis occur in individuals with underlying illness. The incidence also increases with age and increasing comorbidities. Other risk factors for sepsis include immunocompromised state and indwelling vascular or mechanical devices. The most common source of infection in individuals with sepsis is the lungs, accounting for 64% of cases of sepsis. Microbial invasion of the bloodstream is not required for an individual to develop the systemic response that leads to multiorgan dysfunction in sepsis. Blood cultures are only positive in 40–70% of cases of septic shock and approximately 20–40% of cases of severe sepsis. When a culture is positive from any site, the most common organisms are gram-negative bacteria (62%), with *Pseudomonas aeruginosa* and *Escherichia coli* being the most common. Gram-positive bacteria are present in approximately 47% of cases, and 19% occurred in people infected with fungi. Because the numbers add up to >100%, it should be noted that multiple bacteria may be implicated in sepsis.

V-76. **The answer is B.** *(Chap. 297)* Mortality in sepsis remains high, with approximately 20–35% of individuals dying when severe sepsis is present and up to 60% dying due to septic shock. Mortality increases with increasing age and number of comorbidities. Numerous interventions have been attempted to try to decrease mortality by providing better supportive care or targeting the underlying pathophysiologic mechanisms that lead to organ failure in sepsis. An example of a supportive measure that has been proven ineffective in sepsis is insulin therapy to achieve tight glucose control. The rationale for lower blood glucose in sepsis was that hyperglycemia was associated with poorer outcomes in critical illness. After initial enthusiasm from data generated by a single-center trial in a surgical intensive care unit, the benefits were not demonstrated in a medically ill population. Meta-analyses have concluded that intensive insulin therapy does not affect survival and may lead to harm, particularly from hypoglycemia. Anemia also frequently develops in individuals with critical illness. The target hemoglobin necessary to maintain oxygen-carrying capacity has to be balanced against potential harm from transfusion therapy, including infection and transfusion-associated acute lung injury. A randomized trial demonstrated that patients were not harmed by a lower hemoglobin threshold for transfusion (7 g/dL) compared with a higher hemoglobin goal (9 g/dL). Patients with refractory hypotension in sepsis have been shown to have a relative deficiency of cortisol in the face of profound metabolic stress. This so-called critical illness–related corticosteroid insufficiency may lead to worse outcomes in critical illness. Trials were conducted to determine which patients would most benefit from corticosteroid replacement used adrenocorticotropic hormone stimulation to assess adrenal response to stimulus. However, this approach did not lead to improved outcomes, and most practitioners favor a more empirical approach to corticosteroid replacement. Hydrocortisone should be considered at a dose of 50 mg every 6 hours in patients with septic shock on vasopressors. If clinical improvement occurs with use of hydrocortisone over 24–48 hours, then a course of therapy for 5–7 days is indicated. Other interventions that have been tried but failed for septic shock include endotoxin-neutralizing proteins, inhibitors of cyclooxygenase or nitric oxide synthase, anticoagulants, polyclonal antibodies, and inhibitors of tumor necrosis factor-α, interleukin-1, platelet-activating factor, and tissue factor pathway. One of the most widely known medications used for sepsis was recombinant activated protein C (APC). This medication was approved by the U.S. Food and Drug Administration for severe sepsis and septic shock based on the outcome of a randomized controlled trial that showed a mortality benefit in patients who were more severely ill. Subsequent trials showed no benefit in patients with less severe illness and in children. A subsequent confirmatory trial showed no benefit to APC, and it was removed from the market 10 years after being approved.

V-77. **The answer is B.** *(Chap. 297)* This patient has sepsis based on the presence of pneumonia as well as several signs of organ dysfunction. The most recent definition of sepsis simplifies the diagnosis into two categories: sepsis and septic shock. This eliminates prior categories included in the continuum of sepsis including systemic inflammatory response syndrome (SIRS) and severe sepsis. SIRS criteria may be present in many individuals with infection who do not develop progressive symptoms of sepsis. The symptoms that may indicate a harmful systemic response to infection are many of those previously included in the SIRS definition, including fever or hypothermia, tachypnea, tachycardia, and leukocytosis. However, SIRS can be present due to systemic inflammatory responses with other stresses such as trauma or acute pancreatitis that are not caused by infection. Thus, the term SIRS is neither sensitive nor specific for identifying patients at risk of developing sepsis. Severe sepsis was also a term with limited specificity and did not provide additional risk stratification. In the simplified definition, there is greater reliance on the use of the Sequential Organ Failure Assessment (SOFA) score. Sepsis is thus defined as a suspected or documented infection with an acute increase of ≥2 points, whereas septic shock is clinically defined as sepsis with need for vasopressor support and elevated lactate (>2 mmol/L) despite adequate fluid resuscitation. The SOFA score incorporates a variety of measures to determine the magnitude of multiorgan dysfunction. Variables include PaO_2/FiO_2 ratio, platelet count, bilirubin, Glasgow Coma Scale score, creatinine, urine output, and blood pressure/vasopressor support. Sepsis is identified as evidence of infection with evidence of organ dysfunction. Using the SOFA score as a determinant of organ dysfunction creates a more standard measure for identifying sepsis. The criteria for septic shock include (1) sepsis plus (2) the need for vasopressor therapy to elevate mean arterial pressure ≥65 mmHg, with (3) a serum lactate concentration >2.0 mmol/L after adequate fluid resuscitation. A patient may be considered in refractory septic shock if the mean arterial pressure remains low for >1 hour despite fluid resuscitation and vasopressors. Refractory septic shock is not included in the guidelines.

V-78. **The answer is E.** *(Chap. 297)* This patient has neutropenic fever with sepsis and needs broad antibiotic coverage. Since he has an indwelling peripherally inserted central catheter line, he should receive coverage for methicillin-resistant *Staphylococcus aureus* with vancomycin until further data allow potential narrowing of antibiotics. He does not have septic shock and so does not yet require empiric antifungal coverage and the additional of an aminoglycoside. Table V-78 provides a general approach to empiric antibiotic coverage in patients with suspected sepsis.

TABLE V-78 Initial Antimicrobial Therapy for Severe Sepsis with No Obvious Source in Adults with Normal Renal Function

Clinical Condition	Antimicrobial Regimens[a]
Septic shock (immunocompetent adult)	The many acceptable regimens include (1) piperacillin-tazobactam (3.375–4.5 g q6h), (2) cefepime (2 g q12h), or (3) meropenem (1 g q8h) or imipenem-cilastatin (0.5 g q6h). If the patient is allergic to b-lactam antibiotics, use (1) aztreonam (2 g q8h) or (2) ciprofloxacin (400 mg q12h) or levofloxacin (750 mg q24h). Add vancomycin (loading dose of 25–30 mg/kg, then 15–20 mg/kg q8–12h) to each of the above regimens.
Neutropenia (<500 neutrophils/μL)	Regimens include (1) cefepime (2 g q8h), (2) meropenem (1 g q8h) or imipenem-cilastatin (0.5 g q6h) or doripenem (500 mg q8h), or (3) piperacillin-tazobactam (3.375 g q4h). Add vancomycin (as above) if the patient has a suspected central line–associated bloodstream infection, severe mucositis, skin/soft tissue infection, or hypotension. Add tobramycin (5–7 mg/kg q24h) plus vancomycin (as above) plus caspofungin (one dose of 70 mg, then 50 mg q24h) if the patient has severe sepsis/septic shock.
Splenectomy	Use ceftriaxone (2 g q24h, or—in meningitis—2 g q12h). If the local prevalence of cephalosporin-resistant pneumococci is high, add vancomycin (as above). If the patient is allergic to b-lactam antibiotics, use levofloxacin (750 mg q24h) or moxifloxacin (400 mg q24h) plus vancomycin (as above).

[a] All agents are administered by the IV route.

Source: Data from Gilbert DN et al: *The Sanford Guide to Antimicrobial Therapy*, 47th ed, Antimicrobial Therapy, 2017 and Kasper DL et al: *Harrison's Principles of Internal Medicine*, 19th ed. New York: McGraw Hill, 2015.

V-79. **The answer is C.** *(Chap. 298)* This patient is in acute cardiogenic shock. The physical examination clues of low blood pressure and narrow pulse pressure, tachycardia, pulmonary congestion, and an S3 gallop all indicate a low cardiac output, high filling pressure state. The historical data of a preceding viral illness suggest the possibility of a viral, or lymphocytic myocarditis as etiology. In states of undifferentiated shock or severe cardiogenic shock, pulmonary artery catheter guidance may be clinically useful. Pulmonary arterial, or mixed venous, oxygen saturation is indicative and correlative with cardiac output as demonstrated by Fick's formula:

$$\text{Cardiac output} = \text{Oxygen Consumption}/([\text{Arterial Oxygen Content}] - [\text{Mixed Venous Oxygen Content}])$$

This patient has a normal hemoglobin and arterial saturation of 98%. Thus, we would expect mixed venous oxygen content to be reduced, correlating with his examination suggestive of low cardiac output and cardiogenic shock. The mixed venous oxygen saturation is reduced because with the low cardiac output cells will extract more oxygen to maintain normal metabolism. Both A and C are incorrect as we anticipate this patient having low cardiac output and reduced stroke volume. Oxygen saturations drawn from the pulmonary capillary wedge position should represent left atrial or arterial oxygenation, which we know by pulse oximetry is normal in this patient, thus D is incorrect. In states of cardiogenic shock, systemic vascular resistance is elevated indicated in this patient's examination by his narrow pulse pressure and cool extremities.

V-80. **The answer is D.** *(Chap. 298)* This patient is suffering from pulmonary edema, likely due to continuous IV saline infusion. During the 48 hours of her stay, she has received approximately 9.6 L of normal saline which contains more than 8.5 g of sodium chloride (900 mg of NaCl per liter of water in 0.9% saline). Her elevated jugular venous pulse and pulmonary rales indicate pulmonary edema and elevated intracardiac filling pressures. Treatment for acute pulmonary edema includes diuretics (option B), venodilation with nitroglycerin or morphine (options E and C), and discontinuation of IV fluids (option A). Antibiotics (option D) are not indicated now.

V-81. **The answer is B.** *(Chap. 300)* The MRI images show a large left-sided subdural hematoma with compression of the upper midbrain and lower thalamic regions. The regions are displaced away from the mass, and there is transtentorial uncal herniation of the medial temporal lobe. Cerebral herniation occurs when brain is displaced by an adjacent mass into a contiguous compartment that it does not occupy. There are several types of brain herniation: uncal, central, transfalcical, and foraminal. The most common type is uncal herniation, which occurs when the brain is displaced across the tentorium from the supratentorial to infratentorial compartment. The uncus (anterior medial temporal gyrus) moves into the tentorial opening just anterior and adjacent to the midbrain. This causes compression of the ipsilateral third nerve with subsequent enlargement of the ipsilateral pupil. Coma is caused by compression of the midbrain against the opposite tentorial edge. Lateral displacement of the midbrain may also cause compression of the opposite cerebral peduncle causing a contralateral hemiparesis and Babinski sign. Central transtentorial herniation causes a symmetric displacement of the thalamic structures through the tentorial opening, compressing the midbrain. Miotic pupils and decreased alertness occur as opposed to enlargement of a single pupil with uncal herniation. As both central and uncal herniation progress, there is a similar progression of clinical signs with progressive dysfunction of the midbrain, pons, and finally, the medulla. Transfalcical herniation occurs when cingulate gyrus is displaced under the falx and across the midline. Foraminal herniation occurs when the cerebellar tonsils are forced into the foramen magnum resulting in rapid death due to compression of the respiratory center.

V-82. **The answer is E.** *(Chap. 300)* Brain death refers to the irreversible loss of all cerebral and brainstem function. Cardiac activity is preserved, and respiration is maintained only by artificial means. In Western society, brain death is considered equivalent to death, and the respirator can be disconnected to allow cardiac death to occur. Careful examination of a patient needs to be performed to assess when brain death has occurred. At the time of examination, the patient needs to be normothermic and have been without treatment with sedative medications for at least 6–24 hours. Patients should also be maintaining a systolic blood pressure >100 and be euvolemic. Ideal criteria are simple, can be assessed at the bedside, and should have no chance of diagnostic error. Three essential elements of brain death include:

1. Widespread cortical destruction identified by coma and unresponsiveness to all stimuli.
2. Global brainstem damage evidenced by absent pupillary light reflexes and loss of oculovestibular and corneal reflexes.
3. Loss of medullary function with complete and irreversible apnea.

The pupils are usually midsized, but can be enlarged. However, they should not be miotic. Deep tendon reflexes may be present, and Babinski response is usually absent or flexor. The apnea test is performed by preoxygenating a patient with 100% O_2 for up to 10 minutes, with oxygen delivered via transtracheal cannula throughout the test. The patient remains off the ventilator for 8–10 minutes, and signs of respiration are observed. At the end of the test, an arterial blood gas is performed to demonstrate that $PaCO_2$ has risen to 50–60 mmHg. Apnea is confirmed if there is no evidence of respiration when the $PaCO_2$ has risen to a level that should have stimulated respiration. The apnea test should be terminated if the patient develops cardiovascular instability. Other ancillary tests are sometimes performed in patients who cannot undergo clinical testing of brain death. Examples of scenarios in which ancillary tests may be useful include patients who are hemodynamically unstable, patients with diseases causing baseline carbon dioxide retention, and in the presence of prior sedation or neuromuscular blocking agents. The purpose of ancillary testing is to demonstrate lack of cerebral blood flow, and ancillary testing can include radionuclide brain imaging, cerebral angiography, and/or transcranial Doppler measurements.

V-83. **The answer is D.** *(Chap. 300)* A right frontal lobe seizure would cause conjugate eye deviation away from the side of the seizure. For stroke and hemorrhage, in general the eyes look toward a hemispheric lesion and away from a pontine lesion. Uncal herniation from a right-sided lesion would be expected to cause a unilateral third nerve palsy on the side of the lesion. Hepatic encephalopathy might cause nystagmus but should not cause conjugate gaze deviation.

V-84. **The answer is D** *(Chap. 300)* Coma is defined as a sleeplike state with eyes closed from which the patient cannot be aroused. Coma is at the extreme end of the spectrum of a number of disorders that cause impaired consciousness. Catatonia is a hypomobile and mute syndrome that occurs usually as part of a major psychosis, typically schizophrenia or major depression. The vegetative state signifies an awake-appearing but nonresponsive state often in a patient who has emerged from coma.

V-85. **The answer is B.** *(Chap. 301)* Monitoring intracranial pressure (ICP) is an important tool in the care of selected critically ill patients due to neurologic injury or disease. ICP can be monitored by ventriculostomy, intraparenchymal transducer, epidural catheter, or subarachnoid catheters. Epidural or subarachnoid catheters are less reliable and are less frequently used. Ventriculostomy is considered the "gold standard" for ICP monitoring because it offers the advantage of providing a means of cerebrospinal fluid drainage in the event of elevated ICP. In addition, ventriculostomy monitoring also provides greater accuracy because it has the ability to be recalibrated, whereas the intraparenchymal monitor does not. Patients who are most likely to be considered for ICP monitoring are those with severe primary neurologic disorders, including severe traumatic brain injury (Glasgow Coma Scale ≤8), large tissue shifts from supratentorial ischemic or hemorrhagic stroke, intraventricular hemorrhage, or posterior fossa stroke. Individuals with fulminant hepatic failure are also at risk for severe cerebral edema leading to herniation. ICP monitoring is recommended for these individuals, although intraparenchymal monitoring is often more appropriate than ventriculostomy due to the presence of coagulopathy. These patients are at particularly high risk of bleeding. In addition, individuals with diffuse cerebral edema, such as in fulminant hepatic failure, typically have small ventricles leading to difficulty in placement.

V-86. **The answer is D.** *(Chap. 301)* The primary goal of intracranial pressure (ICP) monitoring in patients with severe neurologic injury and elevated ICP is to maintain adequate cerebral perfusion pressure (CPP). CPP is calculated as mean arterial pressure minus the ICP, and the goal CPP is ≥60 mmHg. Normal ICP is <20 mmHg. Thus, this patient is showing evidence of marked elevations in ICP with a CPP of 58 mmHg. When ICP remains elevated for more than 5 minutes, therapy should be undertaken to decrease the ICP. It is important to consider the underlying cause of ICP in an individual when determining treatment plan. In patients with hydrocephalus or subarachnoid hemorrhage, draining cerebrospinal fluid via the ventriculostomy will decrease the ICP. In patients with more diffuse cerebral edema from head trauma or stroke, medical approaches are more appropriate. This patient has hydrocephalus due to subarachnoid bleeding. Therefore, the first line of treatment should be to drain the ventriculostomy. If this fails to adequately alleviate the elevations in ICP, other treatment modalities including osmolar therapy, sedation, hyperventilation, or vasopressors to increase mean arterial pressure can be considered. There are two osmolar therapies that are frequently used: mannitol or 23.4% saline bolus. Deep sedation may be required, and a variety of agents may be used. Neuromuscular blockade may be used as well. Hyperventilation to drop the $PaCO_2$ to 30–35 mmHg works acutely to drop the ICP, but the effect is limited and short-lasting. Vasopressors can be considered to increase the mean arterial pressure and thus ensure an improved CPP. Glucocorticoids are best used in individuals with vasogenic edema from tumor or abscess. In those with refractory elevations in ICP, decompressive craniectomy, high-dose barbiturate therapy, or hypothermia may also be employed.

V-87. **The answer is C.** *(Chap. 301)* Therapeutic hypothermia refers to the purposeful induction of hypothermia to temperatures of 32–34°C (89.6–93.2°F), and it is primarily used following cardiac arrest. The rationale for the use of therapeutic hypothermia is to provide a neuroprotective effect to limit neuronal cell injury and death following a substantial hypoxic insult. Initially, two trials suggested that use of therapeutic hypothermia would improve functional outcomes in patients who remained comatose after resuscitation from cardiac arrest. Subsequent trials showed no significant difference in neurologic outcomes if the temperature was maintained at 32°C (89.6°F) or 36°C (96.8°F) so long as development of fever was prevented. The higher temperature goal was associated with more episodes of a temperature >37°C (98.6°F). Treatment guidelines currently support therapeutic hypothermia for 12–24 hours when the initial rhythm was ventricular fibrillation. Although cerebral edema is a common complication of cardiac arrest and a leading cause of death, there is no recommendation to perform head imaging prior to initiating therapeutic hypothermia. Complications of therapeutic hypothermia include coagulopathy and increased risk of infection.

V-88. **The answer is C.** *(Chap. 301)* Cerebral perfusion pressure is defined as the mean systemic arterial pressure minus the ICP, and provides the driving force for circulation across the capillary beds of the brain. Autoregulation refers to the physiologic response whereby cerebral blood flow (CBF) is regulated via alterations in cerebrovascular resistance to maintain perfusion over wide physiologic changes such as neuronal activation or changes in hemodynamic function (Figure V-88). CBF is only proportional to perfusion pressure at the extremes, since autoregulation provides for a relatively constant blood flow in most situations. Autoregulation occurs in the microcirculation and is mediated by vessels below the resolution of those seen on angiography. CBF is also strongly influenced by pH and $PaCO_2$. CBF increases with hypercapnia and acidosis and decreases with hypocapnia and alkalosis because of pH-related changes in cerebral vascular resistance.

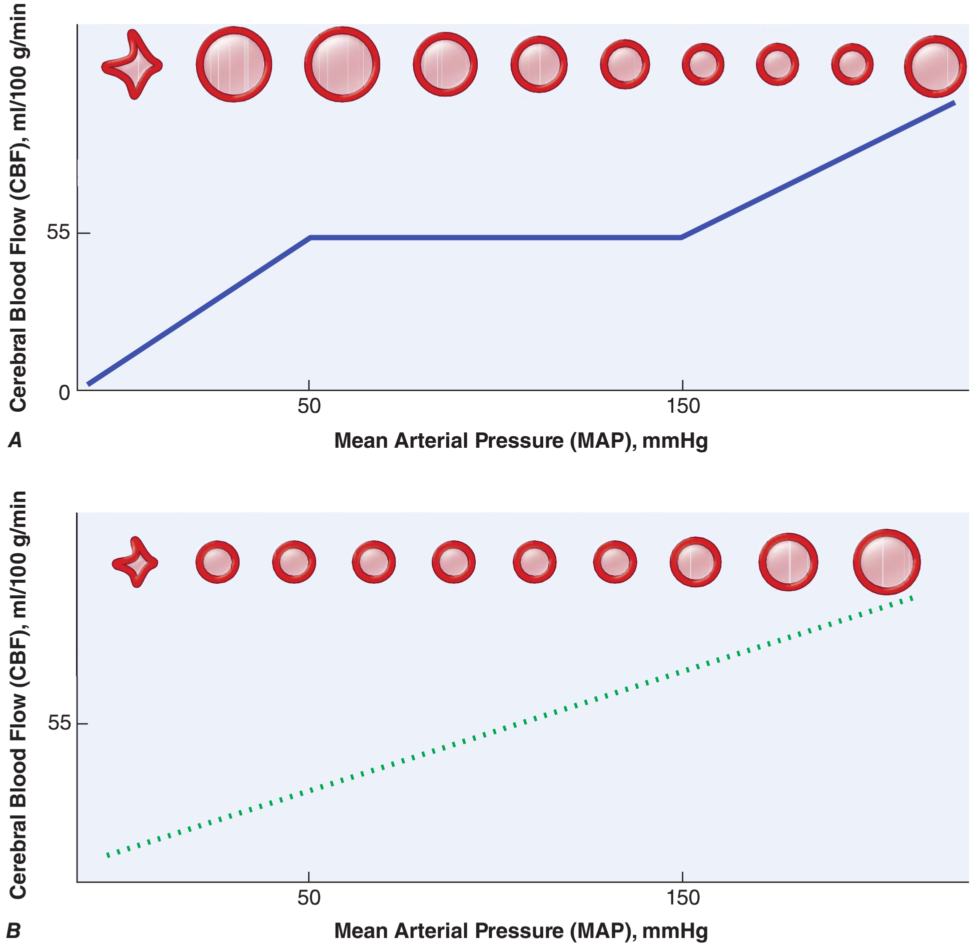


FIGURE V-88

V-89. **The answer is B.** *(Chap. 301)* This patient likely has Wernicke encephalopathy. This syndrome is most common in alcoholics and results from thiamine deficiency. Thiamine is a cofactor of several enzymes, including transketolase, pyruvate dehydrogenase, and α-ketoglutarate dehydrogenase. Thiamine deficiency produces a diffuse decrease in cerebral glucose utilization and results in mitochondrial damage. Glutamate accumulates due to impairment of α-ketoglutarate dehydrogenase activity and, in combination with the energy deficiency, may result in excitotoxic cell damage. IV administration of dextrose in patients at risk for Wernicke encephalopathy may precipitate the syndrome or worsen its manifestations due to an increase in thiamine metabolism. IV thiamine should be given before dextrose in patients at risk for Wernicke encephalopathy. Osmotic demyelination syndrome would not explain his current symptoms. This usually occurs after a rapid increase in serum sodium in patients with severe hyponatremia. Since this patient's hyponatremia has not yet been treated, it would not explain his current symptoms. While chronic alcohol use can certainly cause neuropathy and ataxia, the current suite of symptoms suggests that Wernicke encephalopathy from thiamine deficiency is more likely at play. The potential for some degree of reversibility with administration of IV thiamine should prompt consideration of this condition in alcoholics presenting with any combination of altered mental status, ataxia, and ophthalmoplegia.

V-90. **The answer is A.** *(Chap. 301)* He likely has posterior reversible encephalopathy syndrome caused by endothelial dysfunction from his calcineurin inhibitor. The fluid-attenuated inversion recovery MRI shows increased signal bilaterally in the occipital lobes predominantly involving the white matter, consistent with a hyperperfusion state. Several seemingly diverse syndromes including hypertensive encephalopathy, eclampsia, postcarotid endarterectomy syndrome, and toxicity from calcineurin-inhibitor and other medications share the common pathogenesis of hyperperfusion likely due to endothelial dysfunction. Vasogenic edema is typically the primary process leading to neurologic dysfunction and this is thought to result from one of two mechanisms: exceeding the cerebral autoregulatory threshold leading to increased cerebral blood flow and capillary leakage into the interstitium, or direct impairment of the blood-brain barrier itself. The predilection of all of the hyperperfusion disorders to affect the posterior rather than anterior portions of the brain may be due to a lower threshold for autoregulatory breakthrough in the posterior circulation or a vasculopathy that is more common in these blood vessels. This likely explains his cortical blindness since he has involvement of the bilateral occipital lobes. JC virus can cause encephalopathy in patients on immunosuppression but would not cause the MRI findings seen in this particular patient. While hypertensive emergency can cause hyperperfusion injury, his current blood pressure is similar to his baseline blood pressure making it unlikely that he has exceeded his cerebral autoregulatory threshold to cause cerebral edema. While acute tacrolimus toxicity can occur with normal serum drug levels, it would not be expected to cause the MRI findings seen in this case. The findings on MRI are not consistent with an infarct and are most consistent with a hyperperfusion injury.

V-91. **The answer is E.** *(Chap. 301)* This patient has signs of severe proximal muscle weakness, which makes critical illness polyneuropathy and Guillain-Barré syndrome unlikely. While new onset myasthenia could explain weakness in an intensive care unit patient, problems at the neuromuscular junction are usually the result of medications, in particular neuromuscular blocking agents. Prolonged neuromuscular blockade does not appear to produce permanent damage to the peripheral nervous system. Once the offending medications are discontinued, full strength is restored, although this may take days. However, in this patient the combination of neuromuscular blockade and high-dose corticosteroids may have resulted in a thick-filament myopathy. This muscle disorder is not due to prolonged action of nondepolarizing neuromuscular blocking agents at the neuromuscular junction; rather, it is an actual myopathy with muscle damage. It has occasionally been described with high-dose glucocorticoid use or sepsis alone. Clinically this syndrome is most often recognized when a patient fails to wean from mechanical ventilation despite resolution of the primary pulmonary process. Pathologically, there may be loss of thick (myosin) filaments. Thick-filament critical illness myopathy has a good prognosis. If patients survive their underlying critical illness, the myopathy invariably improves and most patients return to normal. However, because this syndrome is a result of true muscle damage, not just prolonged blockade at the neuromuscular junction, this process may take weeks or months, and tracheotomy with prolonged ventilatory support may be necessary. Some patients do have residual long-term weakness, with atrophy and fatigue limiting ambulation.

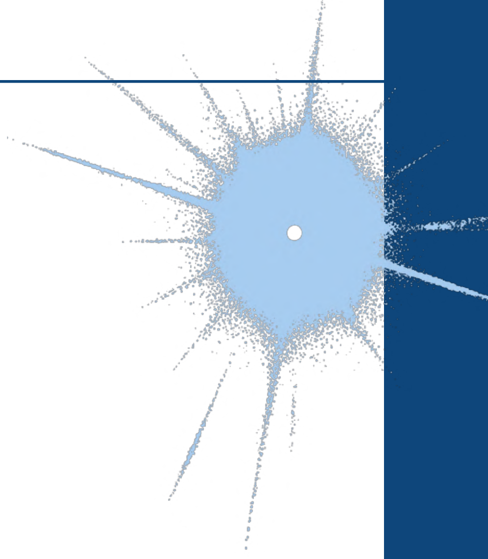
V-92 and V-93. **The answers are E and E, respectively.** *(Chap. 302)* Nontraumatic subarachnoid hemorrhage (SAH) occurs most often following rupture of a saccular, or berry, aneurysm. Autopsy and angiography studies have identified aneurysms in 2% of the adult population, affecting 4 million individuals. The yearly incidence of SAH due to aneurysmal rupture is 20,000–30,000 cases. Many patients die before reaching the hospital. If a patient survives to hospital admission, the 28-day mortality rate is 45%. More than half of individuals who survive have significant neurologic injury with lingering manifestations. The patient with SAH should be admitted to a critical care unit with expertise in managing SAH. Initial treatment of SAH includes early aneurysmal repair while managing intracranial hypertension. Repair of the aneurysm may be accomplished via neurosurgical clipping or endovascular coiling of the aneurysm. Generally coiling has shown improved functional outcomes in those undergoing endovascular procedures. Medical management is complex. Intracranial hypertension is common and frequently requires management with ventriculostomy. Medical management of elevated intracranial pressure is also often required. If a patient survives the initial period following SAH, the patient is vulnerable to several causes of delayed neurologic deficits that typically present within 1–2 weeks after the event. Vasospasm refers to narrowing of the arteries at the base of the brain following SAH and is the most common cause of delayed morbidity and mortality in SAH. Signs of ischemic injury and change in neurologic examination herald the development of vasospasm. Nimodipine is typically prescribed at a dose of 60 mg every 4 hours on admission to the intensive care unit to attempt to prevent vasospasm. Vasospasm can be detected by x-ray angiography or transcranial Doppler ultrasound. Surveillance for vasospasm is often performed via transcranial Doppler ultrasound on a daily or every-other-day basis. In addition to nimodipine, management of acute vasospasm includes raising cerebral perfusion pressure and volume expansion. Phenylephrine and norepinephrine are the most frequently used vasopressors. If vasospasm is refractory to these treatments, intra-arterial vasodilators and/or percutaneous transluminal angioplasty should be considered. Other causes of delayed neurologic deficits following SAH include rerupture of the aneurysm, hydrocephalus, and hyponatremia. The incidence of rerupture of an aneurysm is ~30% in the first month after presentation, with a peak incidence within the first 7 days. Mortality associated with rerupture is 60%. Early endovascular coiling or surgical clipping of the aneurysm decreases the incidence of re-rupture. Hydrocephalus can occur acutely or subacutely after SAH. Subacute development of hydrocephalus is more common and presents over a few days or weeks with progressive drowsiness, incontinence, and slowed mentation. The patient in this scenario had a CT scan that did not show increasing blood, cerebral edema, or development of hydrocephalus. Hyponatremia occurs following SAH due to natriuresis and volume depletion. Electrolytes are typically assessed at least twice daily following SAH as hyponatremia can develop fairly acutely.

V-94. **The answer is E.** *(Chap. 302)* Hyponatremia may be profound and can develop quickly in the first 2 weeks following subarachnoid hemorrhage (SAH). There is both natriuresis and volume depletion with SAH, so that patients become both hyponatremic and hypovolemic. Both atrial natriuretic peptide and brain natriuretic peptide have a role in producing this "cerebral salt-wasting syndrome." Typically, it clears over the course of 1–2 weeks and, in the setting of SAH, should not be treated with free water restriction as this may increase the risk of stroke. Free water restriction is contraindicated in patients with SAH at risk for delayed cerebral ischemia because hypovolemia and hypotension may occur and precipitate cerebral ischemia. Many patients continue to experience a decline in serum sodium despite receiving parenteral fluids containing normal saline. Frequently, supplemental oral salt coupled with normal saline will mitigate hyponatremia, but often patients also require IV hypertonic saline.

V-95. **The answer is E.** *(Chap. 302)* Her presentation is concerning for a subarachnoid hemorrhage (SAH). At the moment of aneurysmal rupture with major SAH, the intracranial pressure suddenly rises. This may account for the sudden transient loss of consciousness that occurs in nearly half of patients. Sudden loss of consciousness may be preceded by a brief moment of excruciating headache, but most patients first complain of headache on regaining consciousness. In 10% of cases, aneurysmal bleeding is severe enough to cause loss of consciousness for several days. In approximately 45% of cases, severe headache associated with exertion is the presenting complaint. The patient often calls the headache "the worst headache of my life"; however, the most important characteristic is sudden onset. Occasionally, these ruptures may present as headache of only moderate intensity or as a change in the patient's usual headache pattern. The headache is usually generalized, often with neck stiffness, and vomiting is common. Although sudden headache in the absence of focal neurologic symptoms is the hallmark of aneurysmal rupture, focal neurologic deficits may occur. Anterior communicating artery or middle cerebral artery bifurcation aneurysms may rupture into the adjacent brain or subdural space and form a hematoma large enough to produce mass effect. The deficits that result can include hemiparesis, aphasia, and mental slowness (abulia). Occasionally, prodromal symptoms suggest the location of a progressively enlarging unruptured aneurysm. A high-quality head CT will demonstrate 95% of SAHs. A thunderclap headache could mimic an SAH. However, before proceeding with treatment for a thunderclap headache, the possibility of an SAH should be investigated. Patients with high suspicion of SAH and a negative CT should receive a lumbar puncture that may demonstrate blood or xanthochromic cerebrospinal fluid.

SECTION VI

Disorders of the Kidney and Urinary Tract



QUESTIONS

DIRECTIONS: Choose the one best response to each question.

VI-1. Which segment of the kidney reabsorbs the highest percentage of filtered sodium chloride?

A. Collecting duct
B. Distal convoluted tubule
C. Loop of Henle
D. Proximal convoluted tubule

VI-2. A 33-year-old woman with recently treated acute myelogenous leukemia now in remission is admitted to the hospital with lethargy, fever, and tachycardia. Blood cultures grow *Pseudomonas* that is resistant to cefepime. She is started on IV gentamicin. Five days after starting gentamicin, her serum creatinine rises from her baseline of 1.0 mg/dL to 2.4 mg/dL. No red or white cell casts are seen on her urinalysis. Her magnesium level is decreased at 1.5 mg/dL. Renal ultrasound is unremarkable with no hydronephrosis. Which of the following is the most likely mechanism of her acute kidney injury?

A. Acute interstitial nephritis
B. Acute tubular necrosis
C. Glomerulonephritis
D. Ischemic injury
E. Obstruction

VI-3. Which of the following laboratory abnormalities typically can be seen accompanying acute kidney injury?

A. Hypercalcemia
B. Hypokalemia
C. Hyponatremia
D. Hypophosphatemia
E. Metabolic alkalosis

VI-4. Which of the following procedures has the highest risk for postoperative acute kidney injury?

A. Anterior cruciate ligament repair
B. Cataract removal
C. Coronary artery bypass
D. Thyroidectomy
E. Total hip arthroplasty

VI-5. Which of the following is a potential etiology for ischemic acute renal failure?

A. Apoptosis and necrosis of tubular cells
B. Decreased glomerular vasodilation in response to nitric oxide
C. Increased glomerular vasoconstriction in response to elevated endothelin levels
D. Increased leukocyte adhesion within the glomerulus
E. All of the above

VI-6. A 57-year-old man with a history of diabetes mellitus and chronic kidney disease with a baseline creatinine of 1.8 mg/dL underwent cardiac catheterization for acute myocardial infarction. He is subsequently diagnosed with acute kidney injury related to iodinated contrast. All of the following statements are true regarding his acute kidney injury EXCEPT:

A. Fractional excretion of sodium will be low.
B. His creatinine is likely to peak within 3–5 days.
C. His diabetes mellitus predisposed him to develop contrast nephropathy.
D. Transient tubule obstruction with precipitated iodinated contrast contributed to development of his acute kidney injury.
E. White blood cell casts are likely on microscopic examination of urinary sediment.

VI-7. Which of the following acute kidney injury patients is most likely to have evidence of bilateral hydronephrosis on ultrasound evaluation of the kidneys?

A. A 19-year-old man with purpura fulminans associated with gonococcal sepsis
B. A 37-year-old woman undergoing chemotherapy and radiation for advanced cervical cancer
C. A 48-year-old man with chronic renal insufficiency due to hypertension that received iodinated contrast for an abdominal angiogram
D. A 53-year-old man with *Escherichia coli* 0157:H7–associated thrombotic thrombocytopenic purpura
E. An 85-year-old woman who resides in a nursing home with pyelonephritis and sepsis

VI-8. A 54-year-old man is admitted to the medical intensive care unit with sepsis associated with pneumococcal pneumonia. He requires mechanical ventilation as well as norepinephrine to maintain a mean arterial pressure >60 mmHg. Invasive hemodynamics show adequate left heart filling pressures, and he is not known to have left ventricular dysfunction. On the third hospital day, his urine output drops and creatinine increases to 3.4 mg/dL. Acute tubular injury is diagnosed. Which of the following agents has been shown to improve outcomes associated with his acute tubular injury?

A. Furosemide
B. Bosentan
C. Low-dose dopamine
D. Insulin-like growth factor
E. None of the above

VI-9. It is hospital day 5 for a 65-year-old patient with prerenal azotemia secondary to dehydration. His creatinine was initially 3.6 mg/dL on admission, but it has improved today to 2.1 mg/dL. He complains of mild lower back pain, and you prescribe naproxen to be taken intermittently. By what mechanism might this drug further impair his renal function?

A. Afferent arteriolar vasoconstriction
B. Afferent arteriolar vasodilatation
C. Efferent arteriolar vasoconstriction
D. Proximal tubular toxicity
E. Ureteral obstruction

VI-10. Which of the following is the leading cause of chronic kidney disease in North America?

A. Autosomal dominant polycystic kidney disease
B. Contrast nephropathy
C. Diabetic nephropathy
D. Focal segmental glomerulosclerosis
E. Recurrent renal calculi

VI-11. A 65-year-old man with a history of hypertension, diabetes, and chronic low back pain presents to the clinic for follow-up. His physical examination is unremarkable with no edema or jugular venous distension. Recent laboratory testing shows a decreased glomerular filtration rate of 55 mL/min/1.73 m^2. His hemoglobin A1c is 5.4%. He is currently on metformin, naproxen, and hydrochlorothiazide. What medication change could help slow his progression of chronic kidney disease?

A. Add furosemide
B. Discontinue metformin
C. Discontinue naproxen
D. Substitute lisinopril for hydrochlorothiazide
E. C and D

VI-12. Which of the following patients has the greatest risk of progression to chronic kidney disease?

A. A 30-year-old man with an estimated glomerular filtration rate (GFR) of 50 mL/min/1.73 m^2 and 350 mg/g of persistent albuminuria
B. A 45-year-old man with an estimated GFR of 90 mL/min/1.73 m^2 and <30 mg/g of persistent albuminuria
C. A 55-year-old man with an estimated GFR of 70 mL/min/1.73 m^2 and 100 mg/g of persistent albuminuria
D. A 65-year-old woman with an estimated GFR of 65 mL/ min/1.73 m^2 and <30 mg/g of persistent albuminuria
E. A 75-year-old man with an estimated GFR of 35 mL/min/1.73 m^2 and <30 mg/g of persistent albuminuria

VI-13. In stage V chronic kidney disease, glomerular filtration rate is below which of the following levels?

A. 90 mL/min/1.73 m^2
B. 60 mL/min/1.73 m^2
C. 25 mL/min/1.73 m^2
D. 15 mL/min/1.73 m^2
E. 0 mL/min/1.73 m^2 (anuria)

VI-14. All of the following statements regarding the use of exogenous erythropoietin in patients with chronic kidney disease are true EXCEPT:

A. Exogenous erythropoietin should be administered with a target hemoglobin concentration of 100–115 g/L.
B. Use of exogenous erythropoietin is associated with improved cardiovascular outcomes.
C. Use of exogenous erythropoietin is associated with increased risk of stroke in patients with concomitant type 2 diabetes mellitus.
D. Use of exogenous erythropoietin may be associated with faster progression to the need for dialysis.
E. Use of exogenous erythropoietin is associated with increased incidence of thromboembolic events.

VI-15. A 63-year-old woman with chronic kidney disease is maintained on daily peritoneal dialysis. Her past medical history is notable for hypertension and atrial fibrillation. Her medications include losartan and warfarin. Two days ago, she noticed a small painful nodule on her abdomen that has progressed to involve skin necrosis and ulceration of the abdominal wall (Figure VI-15). All of the following statements regarding her condition are true EXCEPT:

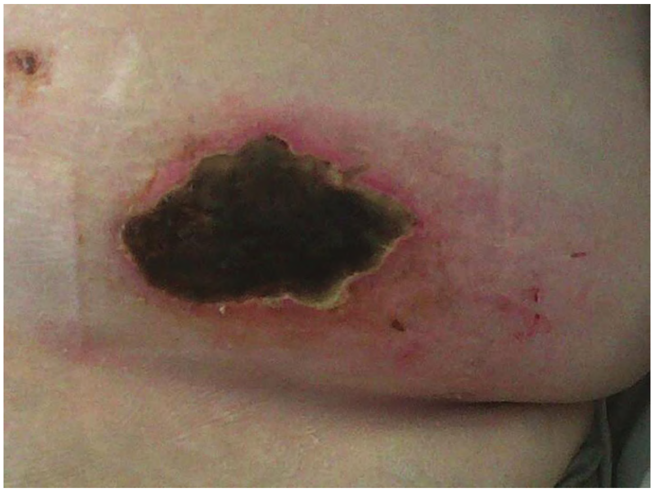


FIGURE VI-15

A. Oral calcium supplement may be a risk factor.
B. Pathologically, there is vascular occlusion.
C. *Pseudomonas* co-infection is typical.
D. Severe hyperparathyroidism may not be present.
E. Warfarin is a risk factor for development of the lesion.

VI-16. Which of the following is the most common acute complication of hemodialysis?

A. Anaphylactoid reactions to dialyzer
B. Bleeding from access site
C. Hypertension
D. Hypotension
E. Muscle cramps

VI-17. A 60-year-old woman with hypertension and type 2 diabetes has recently started peritoneal dialysis due to chronic kidney disease from diabetic nephropathy. Which complications of peritoneal dialysis are of concern for this patient?

A. Hyperkalemia
B. Hyperglycemia
C. Hyperphosphatemia
D. Hypertriglyceridemia
E. B and D

VI-18. A patient is followed closely by her nephrologist for stage IV chronic kidney disease associated with focal segmental glomerulosclerosis. Which of the following is an indication for initiation of maintenance hemodialysis?

A. Acidosis controlled with daily bicarbonate administration
B. Bleeding diathesis
C. Blood urea nitrogen >110 mg/dL without symptoms
D. Creatinine >5 mg/dL without symptoms
E. Hyperkalemia controlled with sodium polystyrene

VI-19. A 35-year-old woman with hypertensive kidney disease progresses to end-stage renal disease. She was initiated on peritoneal dialysis 1 year ago and has done well with relief of her uremic symptoms. She is brought to the emergency department with fever, altered mental status, diffuse abdominal pain, and cloudy dialysate. Her peritoneal fluid is withdrawn through her catheter and sent to the laboratory for analysis. The fluid white blood cell count is 125/μL with 85% polymorphonuclear neutrophils. Which organism is most likely to be found in the culture of the peritoneal fluid?

A. *Candida albicans*
B. *Escherichia coli*
C. *Mycobacterium tuberculosis*
D. *Pseudomonas aeruginosa*
E. *Staphylococcus epidermidis*

VI-20. A 45-year-old woman begins hemodialysis for end-stage renal disease associated with diabetes mellitus. Which of the following is her most likely eventual cause of death?

A. Dementia
B. Major bleeding episode
C. Myocardial infarction
D. Progressive uremia
E. Sepsis

VI-21. Your patient with end-stage renal disease on hemodialysis has persistent hyperkalemia. He has a history of total bilateral renal artery stenosis, which is why he is on hemodialysis. He only has electrocardiogram changes when his potassium rises above 6.0 mEq/L, which occurs a few times per week. You admit him to the hospital for further evaluation. Your laboratory evaluation, nutrition counseling, and medication adjustments have not impacted his serum potassium. What is the next reasonable step to undertake for this patient?

A. Adjust the dialysate
B. Administer a daily dose of furosemide
C. Perform “sodium modeling”
D. Implant an automatic defibrillator
E. Perform bilateral nephrectomy

VI-22. Which of the following medications used for immunosuppression after kidney transplant works by inhibiting purine synthesis and can cause diarrhea as a common side effect?

A. Belatacept
B. Cyclosporine
C. Mycophenolate mofetil
D. Sirolimus
E. Tacrolimus

VI-23. All of the following are considered expanded donor criteria for renal transplantation EXCEPT:

A. Deceased donor >60 years
B. Deceased donor >50 years, hypertension, and creatinine >1.5 mg/dL
C. Deceased donor >50 years, hypertension, and death caused by cerebrovascular accident (CVA)
D. Deceased donor >50 years, death caused by CVA, and creatinine >1.5 mg/dL
E. Presence of antibodies against the donor kidney in the recipient at the time of the anticipated transplantation

VI-24. Which of the following clinical features is characteristic of patients with nephropathy due to type 1 diabetes?

A. Kidney size is reduced
B. Most patients also have diabetic retinopathy
C. Proteinuria is uncommon
D. Renal failure occurs within 1–2 years after the onset of proteinuria
E. Urinalysis shows red blood cell casts

VI-25. All of the following are typical causes of secondary membranous glomerulonephritis EXCEPT?

A. Hepatitis C
B. Malignancy
C. Nonsteroidal anti-inflammatory drug use
D. Systemic lupus erythematosus
E. Tuberculosis

VI-26. A 33-year-old previously healthy woman presents to the emergency department with malaise, confusion, and fever of 37.8°C (100.1°F). She had no preceding diarrheal illness. CT of the head is unremarkable. She is found to have platelets of 13,000/cu, hemoglobin of 9.0 g/dL, and creatinine of 2.3 mg/dL. Urinalysis shows pH 5.0, protein 1+, and 11 red blood cells/high-powered field. Which of the following laboratory findings would be expected with her diagnosis?

A. ADAMSTS13 <10%
B. Anti-glomerular basement membrane antibodies
C. Decreased lactate dehydrogenase
D. Positive direct Coombs test
E. Spherocytes on peripheral blood smear

VI-27. A 21-year-old man is diagnosed with poststreptococcal glomerulonephritis. Which of the following is likely to be found in his urine?

A. >3 g per 24-hour proteinuria without hematuria
B. Macroscopic hematuria and 24-hour urinary albumin of 227 mg
C. Microscopic hematuria with leukocytes and 24-hour urinary albumin of 227 mg
D. Positive urine culture for *Streptococcus*
E. Sterile pyuria without proteinuria

VI-28. A 50-year-old obese female with a 5-year history of mild hypertension controlled by a thiazide diuretic is being evaluated because proteinuria was noted on a urine dipstick during her routine yearly medical visit. Physical examination discloses a height of 167.6 cm (66 inches), weight of 91 kg (202 lb), blood pressure of 130/80, elevated jugular venous pressure, a fourth heart sound, and trace pedal edema. Laboratory values are as follows: serum creatinine 106 μmol/L (1.2 mg/dL), blood urea nitrogen 6.4 mmol/L (18 mg/dL), and creatinine clearance 87 mL/min. Urinalysis shows pH 5.0, specific gravity 1.018, protein 3+, no glucose, and occasional coarse granular cast. Urine protein excretion is 5.9 g/dL. A renal biopsy demonstrates that 60% of the glomeruli, mostly in the corticomedullary junction, have segmental scarring by light microscopy, with the remainder of the glomeruli appearing unremarkable (Figure VI-28). Which of the following is the most likely diagnosis?

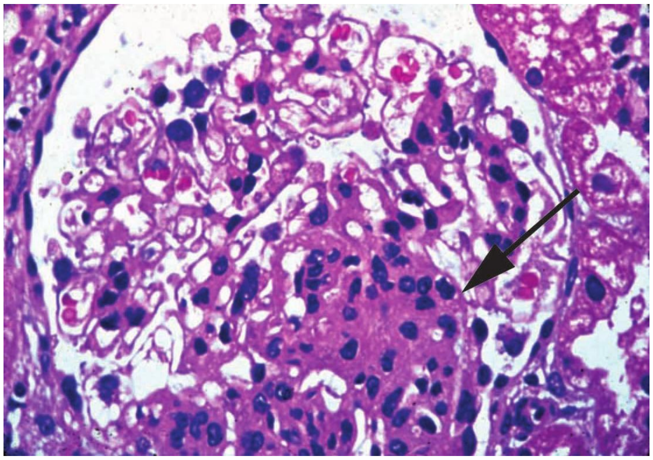


FIGURE VI-28 EGN/UPenn Collection.

A. Focal segmental sclerosis
B. Hypertensive nephrosclerosis
C. Minimal change (nil) disease
D. Membranous glomerulopathy
E. Crescentic glomerulonephritis

VI-29. Which of the following is a genetic disease that can lead to bilateral renal cysts and carries an increased risk of renal cell carcinoma?

A. Medullary sponge kidney
B. Neurofibromatosis type 1
C. Tuberous sclerosis
D. Von Hippel-Lindau disease
E. C and D

VI-30. A 28-year-old woman was recently diagnosed with autosomal dominant polycystic kidney disease after an episode of hematuria. She is concerned about intracranial aneurysm risk. Which of the following statements is true regarding this risk?

A. Family history of ruptured intracranial aneurysms does not increase risk of rupture.
B. Prior intracranial hemorrhage does not increase risk of subsequent hemorrhage.
C. The size of the aneurysm does not correlate with its risk of spontaneous rupture.
D. There is no increased risk of intracranial aneurysm in this condition.
E. Uncontrolled hypertension augments the risk of spontaneous rupture.

VI-31. A 21-year-old male college student is evaluated for profound fatigue that has been present for several years but has recently become debilitating. He also reports several foot spasms and cramps and occasionally sustained muscle contractions that are uncontrollable. He is otherwise healthy, takes no medications, and denies tobacco or alcohol use. On examination, he is well developed with normal vital signs including blood pressure. The remainder of the examination is normal. Laboratory evaluation shows a sodium of 138 mEq/L, potassium of 2.8 mEq/L, chloride of 90 mEq/L, and bicarbonate of 30 mmol/L. Magnesium level is normal. Urine screen for diuretics is negative, and urine chloride is elevated. Which of the following is the most likely diagnosis?

A. Bulimia nervosa
B. Diuretic abuse
C. Gitelman syndrome
D. Liddle syndrome
E. Type 1 pseudohypoaldosteronism

VI-32. A 24-year-old Caucasian man presents to the clinic after being found to have a creatinine of 1.6 mg/dL on routine laboratory studies. The rest of his metabolic panel and blood counts are normal. He has been mostly healthy, with the exception of several urinary tract infections in his childhood. He takes no medications. Urinalysis shows 1+ proteinuria and no red or white blood cells. Renal ultrasound shows decreased size of both kidneys with thinned cortices and regions of compensatory hypertrophy. What is the likely cause of his renal disease?

A. Allergic interstitial nephritis
B. IgG4 disease
C. Reflux nephropathy
D. Sickle cell nephropathy
E. Sjögren syndrome

VI-33. All of the following medications can cause acute interstitial nephritis EXCEPT:

A. Celecoxib
B. Hydromorphone
C. Pantoprazole
D. Penicillin
E. Valproate

VI-34. A patient with a history of Sjögren syndrome has the following laboratory findings: plasma sodium 139 mEq/L, chloride 112 mEq/L, bicarbonate 15 mEq/L, and potassium 3.0 mEq/L. Urine studies show a pH of 6.0, sodium of 15 mEq/L, potassium of 10 mEq/L, and chloride of 12 mEq/L. What is the most likely diagnosis?

A. Chronic diarrhea
B. Type I renal tubular acidosis (RTA)
C. Type II RTA
D. Type III RTA
E. Type IV RTA

VI-35. In which of the following cases would treatment with corticosteroids for biopsy-proven interstitial nephritis be most likely to impact long-term renal recovery?

A. A 37-year-old woman with sarcoidosis
B. A 48-year-old man with slowly progressing interstitial nephritis over 2 months with fibrosis found on biopsy
C. A 54-year-old man with diabetes mellitus and recent *Salmonella* infection
D. A 63-year-old man with allergic interstitial nephritis after cephalosporin antibiotic use
E. None of the above

VI-36. A 58-year-old woman undergoes a hysterectomy and postoperatively develops acute respiratory distress syndrome. She is treated with mechanical ventilation and broad-spectrum antibiotics. Aside from hypothyroidism, she has no underlying medical conditions. On day 5 of her hospitalization, her urine output is noted to fall, and her serum creatinine rises from 1.2 to 2.5 mg/dL. Allergic interstitial nephritis from cephalosporin antibiotics is suspected. Which of the following findings will confirm this diagnosis?

A. Hematuria
B. Peripheral blood eosinophilia
C. Urinary eosinophils on urine microscopy
D. White blood cell casts on urine microscopy
E. None of the above

VI-37. Eculizumab, used in the treatment of atypical hemolytic uremic syndrome, targets which of the following?

A. C5
B. Factor V
C. Interleukin (IL)-6 receptor
D. IL-17
E. Tumor necrosis factor-α

VI-38. A 66-year-old woman presents to the emergency room with malaise, confusion, and headache. Blood pressure is found to be 220/105. Physical examination is notable for skin thickening of the arms and legs, facial telangiectasias, and decreased oral aperture. Laboratory studies show a creatinine of 3.5 mg/dL, hemoglobin of 7.0 g/dL, platelets of 75,000/dL, lactate dehydrogenase of 700. What is the appropriate initial treatment?

A. Amlodipine
B. Captopril
C. Eculizumab
D. Heparin
E. Plasmapheresis

VI-39. A 35-year-old woman presents with complaints of bilateral lower extremity edema, polyuria, and moderate left-sided flank pain that began approximately 2 weeks ago. There is no past medical history. She is taking no medications and denies tobacco, alcohol, or illicit drug use. Examination shows normal vital signs, including normal blood pressure. There is 2+ edema in bilateral lower extremities. The 24-hour urine collection is significant for 3.5 g of protein. Urinalysis is bland except for the proteinuria. Serum creatinine is 0.7 mg/dL, and ultrasound examination shows the left kidney measuring 13 cm and the right kidney measuring 11.5 cm. You are concerned about renal vein thrombosis. What test do you choose for the evaluation?

A. CT of the renal veins
B. Contrast venography
C. Magnetic resonance venography
D. 99Tc-labeled diethylene-triamine-pentaacetate acid (DTPA) imaging
E. Ultrasound with Doppler evaluation of the renal veins

VI-40. A 28-year-old woman who is in the 30th week of her second pregnancy has been followed closely because of mild hypertension. Her first pregnancy was complicated by preeclampsia. She now complains of worsening fatigue over the last day. Her blood pressure is 140/90, and she has a heart rate of 84 beats/min and room air oxygen saturation of 95%. Fetal monitoring shows no distress. Laboratory studies are notable for a hemoglobin of 6 g/dL (10 g/dL 1 week ago) and platelet count of 80,000/dL (180,000/dL 1 week ago). A peripheral blood smear shows schistocytes. All of the following statements are true about her condition EXCEPT:

A. Glucocorticoids are effective in reducing morbidity and mortality.
B. Her liver function enzymes are likely elevated.
C. Preeclampsia predisposes to the condition.
D. Renal failure is common.
E. The condition will likely resolve after delivery of the fetus.

VI-41. Which of the following interventions has been shown to decrease the recurrence of calcium oxalate renal stones?

A. A diet with abundant spinach and rhubarb
B. Aspirin
C. Low-calcium diet (400 mg/day)
D. Thiazide diuretics
E. Vitamin C supplements

VI-42. A 48-year-old man with diabetes mellitus, hyperlipidemia, and atrial fibrillation presents to the emergency department for evaluation of left flank pain and groin pain that has been severe and present for approximately 3 hours. His medications include metformin, atorvastatin, and warfarin. He is uncomfortable and has a temperature of 37°C (98.6°F), heart rate of 105 beats/min, blood pressure of 145/95, respiratory rate of 21 breaths/min, and room air oxygen saturation of 98%. His physical examination is notable for left flank pain but no abdominal organomegaly or focal tenderness. An electrocardiogram shows sinus tachycardia with nonspecific ST-T wave changes. International normalized ratio is 2.0. His renal function is normal, and urine analysis shows many red blood cells, few white blood cells, no bacteria, and no crystals. Which of the following is the preferred diagnostic study?

A. 24-Hour urine collection
B. Cystoscopy
C. MRI
D. Noncontrast CT scan
E. Ultrasound

VI-43. In the patient described above, a noncontrast abdominal CT is performed (Figure VI-43). Which of the following is the most likely diagnosis?

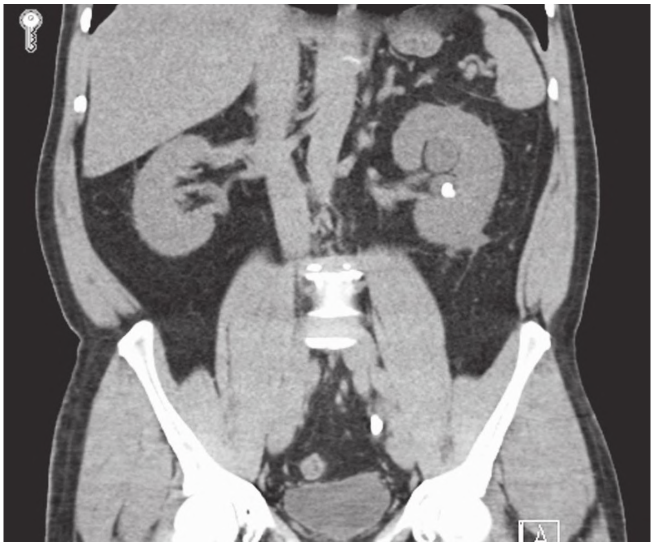


FIGURE VI-43 Used with permission from Dr. Stuart Silverman, Brigham and Women's Hospital.

A. Appendicitis
B. Nephrolithiasis
C. Renal cell carcinoma
D. Pyelonephritis
E. Retroperitoneal hematoma

VI-44. Which of the following fluid or electrolyte abnormalities can be seen in some patients after the relief of bilateral renal obstruction?

A. Hyperkalemia
B. Hypermagnesemia
C. Hypernatremia
D. Hypovolemia
E. C and D

VI-45. A 54-year-old woman with a history of colon cancer treated with resection and chemotherapy 2 years earlier is admitted to the hospital after routine lab work at her primary care physician's office showed a blood urea nitrogen of 65 mg/dL and a creatinine of 4.5 mg/dL. She reports mild fatigue and recent lower back pain, but otherwise feels well. She does admit to recent nonsteroidal anti-inflammatory drug (NSAID) use but has not taken more than the recommended quantity. Aside from stopping the NSAID and avoidance of nephrotoxins, which of the following studies should be the next step?

A. CT of the abdomen/pelvis with oral contrast
B. Postvoid residual volume of bladder
C. Retrograde urography
D. Ultrasound of the abdomen/kidney
E. Urinary fractional excretion of sodium

VI-46. The pain associated with acute urinary tract obstruction is a result of which of the following?

A. Compensatory natriuresis
B. Decreased medullary blood flow
C. Increased renal blood flow
D. Vasodilatory prostaglandins

ANSWERS

VI-1. **The answer is D.** *(Chap. 303)* The proximal tubule is responsible for reabsorbing ~60% of filtered sodium chloride (NaCl) and water, as well as ~90% of filtered bicarbonate and most critical nutrients such as glucose and amino acids. The proximal tubule uses both cellular and paracellular transport mechanisms. The apical membrane of proximal tubular cells has an expanded surface area available for reabsorptive work created by a dense array of microvilli called the *brush border*, and leaky tight junctions enable high-capacity fluid reabsorption. Approximately 15–25% of filtered NaCl is reabsorbed in the loop of Henle, mainly by the thick ascending limb. The distal convoluted tubule reabsorbs ~5% of the filtered NaCl. This segment is composed of a tight epithelium with little water permeability. The collecting duct modulates the final composition of urine. The two major divisions, the cortical collecting duct and inner medullary collecting duct, contribute to reabsorbing ~4–5% of filtered Na^+ and are important for hormonal regulation of salt and water balance.

VI-2. **The answer is B.** *(Chap. 304)* Several antimicrobial agents are commonly associated with acute kidney injury (AKI). Aminoglycosides (e.g., gentamicin) and amphotericin B both cause tubular necrosis. Nonoliguric AKI (i.e., with a urine volume >400 mL/day) accompanies 10–30% of courses of aminoglycoside antibiotics, even when plasma levels are in the therapeutic range. Aminoglycosides are freely filtered across the glomerulus and then accumulate within the renal cortex, where concentrations can greatly exceed those of the plasma. AKI typically manifests after 5–7 days of therapy and can present even after the drug has been discontinued. Hypomagnesemia is a common finding. AKI secondary to acute interstitial nephritis can occur as a consequence of exposure to many antibiotics, including penicillins, cephalosporins, quinolones, sulfonamides, and rifampin. There is no reason for obstructive nephropathy or ischemic injury by history. Renal ultrasound shows no evidence of obstruction. There are no red or white cell casts or anything in the history to suggest glomerulonephritis.

VI-3. **The answer is C.** *(Chap. 304)* A variety of electrolyte abnormalities can be seen in acute kidney injury (AKI) including hyponatremia, hyperkalemia, metabolic acidosis, hyperphosphatemia, and hypocalcemia. Abnormalities in plasma electrolyte composition can be mild or life-threatening. The dysfunctional kidney has limited ability to regulate electrolyte balance. Administration of excessive hypotonic crystalloid or isotonic dextrose solutions can result in hyposmolality and hyponatremia, which, if severe, can cause neurologic abnormalities, including seizures. Marked hyperkalemia is particularly common in rhabdomyolysis, hemolysis, and tumor lysis syndrome due to release of intracellular potassium from damaged cells. Muscle weakness may be a symptom of hyperkalemia. Metabolic acidosis, usually accompanied by an elevation in the anion gap, is common in AKI, and can further complicate acid-base and potassium balance in individuals with other causes of acidosis, including sepsis, diabetic ketoacidosis, or respiratory acidosis. AKI-associated hypocalcemia may also arise from derangements in the vitamin D–parathyroid hormone–fibroblast growth factor-23 axis. Hypocalcemia is often asymptomatic but can lead to perioral paresthesias, muscle cramps, seizures, carpopedal spasms, and prolongation of the QT interval on electrocardiography.

VI-4. **The answer is C.** *(Chap. 304)* Ischemia-associated acute kidney injury (AKI) is a serious complication in the postoperative period, especially after major operations involving significant blood loss and intraoperative hypotension. The procedures most commonly associated with AKI are cardiac surgery with cardiopulmonary bypass (particularly for combined valve and bypass procedures), vascular procedures with aortic cross-clamping, and intraperitoneal procedures. Severe AKI requiring dialysis occurs in ~1% of cardiac and vascular surgery procedures. The risk of severe AKI has been less well studied for major intraperitoneal procedures but appears to be of comparable magnitude. Common risk factors for postoperative AKI include underlying chronic kidney disease, older age, diabetes mellitus, congestive heart failure, and emergency procedures. The pathophysiology of AKI following cardiac surgery is multifactorial. Major AKI risk factors are common in the population undergoing cardiac surgery. The use of nephrotoxic agents, including iodinated contrast for cardiac imaging prior to surgery, may increase the risk of AKI. Cardiopulmonary bypass is a unique hemodynamic state characterized by nonpulsatile flow and exposure of the circulation to extracorporeal circuits. Longer duration of cardiopulmonary bypass is a risk factor for AKI. In addition to ischemic injury from sustained hypoperfusion, cardiopulmonary bypass may cause AKI through a number of mechanisms including extracorporeal circuit activation of leukocytes and inflammatory processes, hemolysis with resultant pigment nephropathy, and aortic injury with resultant atheroemboli. AKI from atheroembolic disease, which can also occur following percutaneous catheterization of the aorta, or spontaneously, is due to cholesterol crystal embolization resulting in partial or total occlusion of multiple small arteries within the kidney. Over time, a foreign body reaction can result in intimal proliferation, giant cell formation, and further narrowing of the vascular lumen, accounting for the generally subacute (over a period of weeks rather than days) decline in renal function.

VI-5. **The answer is E.** *(Chap. 304)* Ischemic acute renal failure has many potential etiologies (Figure VI-5). Microvascular disorders include increased vasoconstriction from endothelin and other mediators, decreased nitric oxide, prostaglandin- or bradykinin-mediated vasodilation, increased endothelial and vascular smooth muscle cell damage, and increased leukocyte adhesion. Tubular factors include cytoskeletal breakdown, loss of polarity, apoptosis and necrosis, desquamation of viable and necrotic cells, tubular obstruction, and back leak. Inflammatory and vasoactive mediators may affect both tubular and microvascular pathophysiologic mechanisms.

VI-6. **The answer is E.** *(Chap. 304)* Iodinated contrast agents that are commonly used in cardiovascular and CT imaging are a major cause of acute kidney injury (AKI). Underlying mechanisms leading to kidney injury include transient tubular obstruction by contrast material, hypoxia in the other renal medulla due to alterations in renal microcirculation and occlusion of small vessels, and cytotoxic damage to the tubules directly or through the generation of free radicals by contrast material. Risk factors for contrast-associated nephropathy include diabetes mellitus, congestive heart failure, pre-existing chronic kidney disease, and multiple myeloma–associated renal failure. Serum creatinine begins to rise at 24–48 hours and will peak at 3–5 days, usually with resolution within a week. Urinary sediment is bland, without casts. The fractional excretion of sodium is low in many cases, particularly early before tubular injury is extensive because of the microvascular source of injury. Other diagnostic agents implicated as a cause of AKI are high-dose gadolinium used for MRI and oral sodium phosphate solutions used as bowel purgatives.

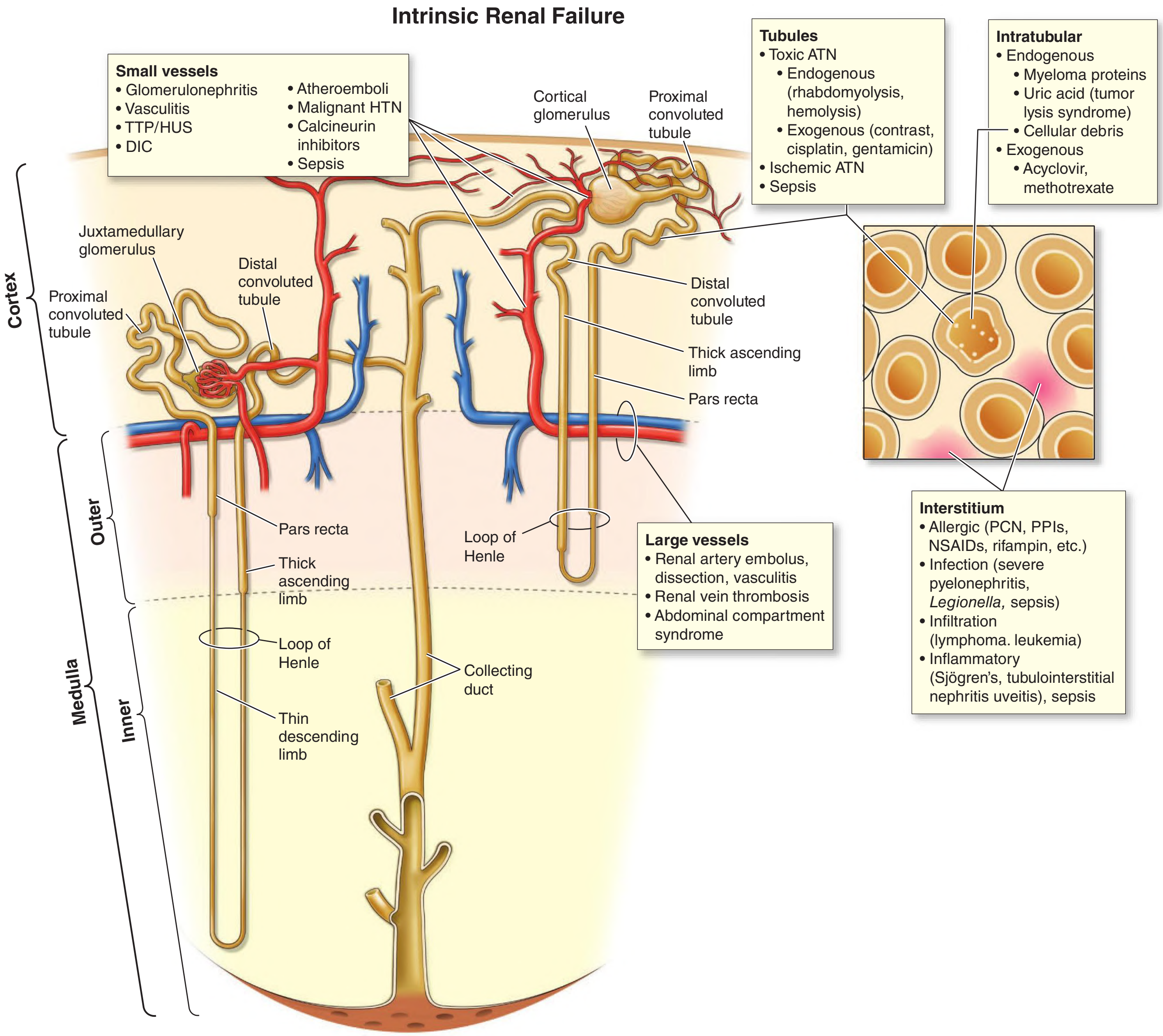

Intrinsic Renal Failure
Small vessels
• Glomerulonephritis
• Vasculitis
• TTP/HUS
• DIC
• Atheroemboli
• Malignant HTN
• Calcineurin inhibitors
• Sepsis
Cortical glomerulus
Proximal convoluted tubule
Tubules
• Toxic ATN
• Endogenous (rhabdomyolysis, hemolysis)
• Exogenous (contrast, cisplatin, gentamicin)
• Ischemic ATN
• Sepsis
Intratubular
• Endogenous
• Myeloma proteins
• Uric acid (tumor lysis syndrome)
• Cellular debris
• Exogenous
• Acyclovir, methotrexate
Cortex
Juxtamedullary glomerulus
Proximal convoluted tubule
Distal convoluted tubule
Distal convoluted tubule
Thick ascending limb
Pars recta
Medulla
Outer
Inner
Pars recta
Thick ascending limb
Loop of Henle
Loop of Henle
Collecting duct
Thin descending limb
Large vessels
• Renal artery embolus, dissection, vasculitis
• Renal vein thrombosis
• Abdominal compartment syndrome
Interstitium
• Allergic (PCN, PPIs, NSAIDs, rifampin, etc.)
• Infection (severe pyelonephritis, *Legionella,* sepsis)
• Infiltration (lymphoma. leukemia)
• Inflammatory (Sjögren's, tubulointerstitial nephritis uveitis), sepsis

FIGURE VI-5 Major causes of intrinsic acute kidney injury. *Abbreviations:* ATN, acute tubular necrosis; DIC, disseminated intravascular coagulation; HTN, hypertension; NSAID, nonsteroidal anti-inflammatory drug; PCN, penicillin; PPI, proton pump inhibitors; TTP/HUS, thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome.

VI-7. **The answer is B.** *(Chap. 304)* Postrenal obstruction is an important and potentially reversible cause of AKI. Ultrasound evaluation of the kidneys classically demonstrates bilateral hydronephrosis, because unilateral obstruction is unlikely to cause kidney injury unless a single functioning kidney is present, chronic kidney disease pre-exists, or, rarely, reflex vasospasm of the unobstructed kidney is present. Advanced cervical cancer with invasion into the urinary system or retroperitoneum is a common cause of obstructive uropathy. Thrombotic thrombocytopenia purpura, disseminated gonococcus with sepsis, and pyelonephritis are intrinsic causes of acute kidney failure and will not cause bilateral hydronephrosis. Neither chronic hypertensive nephropathy nor contrast-induced nephropathy will cause bilateral hydronephrosis.

VI-8. **The answer is E.** *(Chap. 304)* Acute kidney injury (AKI) is a poor prognostic indicator in patients in the intensive care unit, as has been shown in multiple types of intensive care units for multiple medical conditions. Unfortunately, care of critically ill patients with AKI is supportive, because no specific therapy has been shown to improve outcomes. Agents that have specifically been shown to have no benefit in the treatment of acute tubular injury include atrial natriuretic peptide, low-dose dopamine, endothelin antagonists, loop diuretics, calcium channel blockers, α-adrenergic receptor blockers, prostaglandin analogs, antioxidants, insulin-like growth factor, and antibodies against leukocyte adhesion molecules. Volume repletion is critical to ensure adequate perfusion, and diuretics are only indicated in patients with replete fluid status and low urinary flow rates.

VI-9. **The answer is A.** *(Chap. 304)* Nonsteroidal anti-inflammatory drugs (NSAIDs) do not alter glomerular filtration rate in normal individuals. However, in states of mild to moderate hypoperfusion (as in prerenal azotemia) or in the presence of chronic kidney disease, glomerular perfusion and filtration fraction are preserved through several compensatory mechanisms. In response to a reduction in perfusion pressures, stretch receptors in afferent arterioles trigger a cascade of events that lead to afferent arteriolar dilatation and efferent arteriolar vasoconstriction, preserving glomerular filtration fraction. These mechanisms are partly mediated by the vasodilators prostaglandin E2 and prostacyclin. NSAIDs can impair the kidney's ability to compensate for a low perfusion pressure by interfering with local prostaglandin synthesis and inhibiting these protective responses. Ureteral obstruction is not the mechanism by which the NSAID impairs renal function in this scenario. NSAIDs are not known to be proximal tubule toxins.

VI-10. **The answer is C.** *(Chap. 305)* It has been estimated from population data that at least 6% of the adult population in the United States has chronic kidney disease (CKD) at stages 1 and 2. An additional 4.5% of the U.S. population is estimated to have stages 3 and 4 CKD. Table VI-10 lists the five most frequent categories of causes of CKD, cumulatively accounting for >90% of the CKD disease burden worldwide. The relative contribution of each category varies among different geographic regions. The most frequent cause of CKD in North America and Europe is diabetic nephropathy, most often secondary to type 2 diabetes mellitus. Patients with newly diagnosed CKD often have hypertension. When no overt evidence for a primary glomerular or tubulointerstitial kidney disease process is present, CKD is frequently attributed to hypertension. However, it is now appreciated that such individuals can be considered in two categories. The first includes patients with a subclinical primary glomerulopathy, such as focal segmental or global glomerulosclerosis. The second includes patients in whom progressive nephrosclerosis and hypertension is the renal correlate of a systemic vascular disease, often also involving large- and small-vessel cardiac and cerebral pathology.

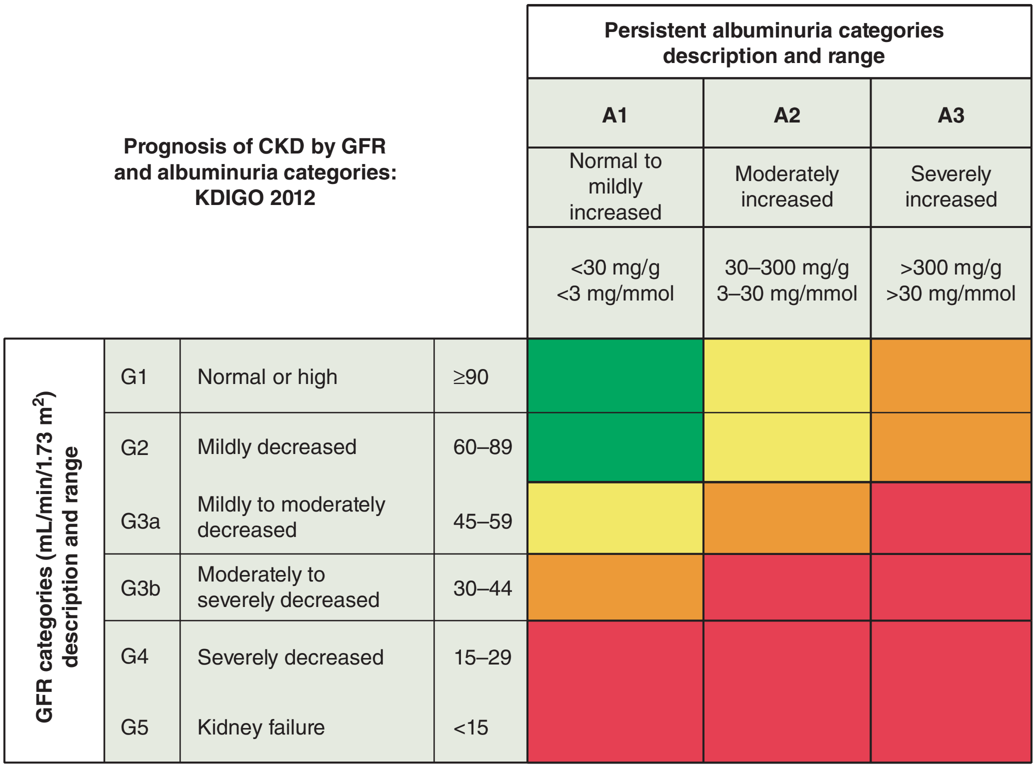
TABLE VI-10 Leading Categories of Etiologies of Chronic Kidney Disease[a]

- Diabetic nephropathy
- Glomerulonephritis
- Hypertension-associated chronic kidney disease (includes vascular and ischemic kidney disease and primary glomerular disease with associated hypertension)
- Autosomal dominant polycystic kidney disease
- Other cystic and tubulointerstitial nephropathy

[a] Relative contribution of each category varies with geographic region and race.

VI-11. **The answer is E.** *(Chap. 305)* It is important to limit exposure to nephrotoxic agents to prevent progression of chronic kidney disease. These include nonsteroidal anti-inflammatory drugs like naproxen and radiographic dye. Avoiding volume depletion is also helpful. This patient had no indication for a diuretic so adding furosemide is not indicated and may lead to volume depletion. Several controlled studies have shown that angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers are effective in slowing the progression of renal failure in patients with advanced stages of both diabetic and nondiabetic chronic kidney disease, in large part through effects on efferent vasodilatation and the subsequent decline in glomerular hypertension. Controlling diabetes is important in managing diabetic nephropathy. His diabetes is well managed with metformin currently, so it should not be discontinued.

VI-12. and VI-13. The answers are A and D, respectively. *(Chap. 305)* Chronic kidney disease (CKD) encompasses a spectrum of different pathophysiologic processes associated with abnormal kidney function and a progressive decline in glomerular filtration rate (GFR). Stages of CKD are stratified by both estimated GFR and the degree of albuminuria to predict risk of progression of CKD. Previously, CKD had been staged solely by the GFR. However, the risk of worsening of kidney function is closely linked to the amount of albuminuria, so it has been incorporated into the classification (Figure VI-13). Note that although age impacts GFR, it is not an independent criterion for risk of progression to CKD. CKD is still staged by GFR. GFR is ≥90 mL/min/1.73 m^2 in stage I, 60–89 mL/min/1.73 m^2 in stage II, 30–59 mL/min/1.73 m^2 in stage III, 15–29 mL/min/1.73 m^2 in stage IV, and <15 mL/min/1.73 m^2 in stage V.



Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012

				Persistent albuminuria categories description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (mL/min/1.73 m^2) description and range	G1	Normal or high	≥90	🟩	🟨	🟧
	G2	Mildly decreased	60–89	🟩	🟨	🟧
	G3a	Mildly to moderately decreased	45–59	🟨	🟧	🟥
	G3b	Moderately to severely decreased	30–44	🟧	🟥	🟥
	G4	Severely decreased	15–29	🟥	🟥	🟥
	G5	Kidney failure	<15	🟥	🟥	🟥

FIGURE VI-13 Kidney Disease Improving Global Outcome (KDIGO) classification of chronic kidney disease (CKD). Gradation of color from green to red corresponds to increasing risk and progression of CKD. *Abbreviation:* GFR, glomerular filtration rate. (Reproduced with permission from Summary of Recommendation Statements. *Kidney Int Suppl* 3:5, 2013.)

VI-14. The answer is B. *(Chap. 305)* Anemia is a common consequence of chronic kidney disease (CKD) and may be multifactorial, with etiologies including relative erythropoietin deficiency, iron deficiency, chronic inflammation, diminished red cell survival, and bleeding diathesis. Several trials of erythropoietin supplementation in patients with CKD have failed to show improved cardiovascular outcomes with this therapy. Indeed, these trials have shown a higher incidence of thromboembolic events and stroke in type 2 diabetics and potentially faster progression to need for dialysis. Because of these concerning findings, erythropoietin use has been altered from prior recommendations, and current practice is to target a hemoglobin concentration of 100–115 g/L.

VI-15. The answer is C. *(Chap. 305)* This patient has calciphylaxis. Calciphylaxis (calcific uremic arteriolopathy) is a devastating condition seen almost exclusively in patients with advanced chronic kidney disease. It is heralded by livedo reticularis and advances to patches of ischemic necrosis, especially on the legs, thighs, abdomen, and breasts. Pathologically, there is evidence of vascular occlusion in association with extensive vascular and soft tissue calcification. It appears that this condition is increasing in incidence. Originally, it was ascribed to severe abnormalities in calcium and phosphorus control in dialysis patients, usually associated with advanced hyperparathyroidism. However, more recently, calciphylaxis has been seen with increasing frequency in the absence of severe hyperparathyroidism. Other etiologies have been suggested, including the increased use of oral calcium as a phosphate binder. Warfarin is commonly used in hemodialysis patients, and one of the effects of warfarin therapy is to decrease the vitamin K–dependent regeneration of matrix GLA protein. The GLA protein is important in preventing vascular calcification. Thus, warfarin treatment is considered a risk factor for calciphylaxis, and if a patient develops this syndrome, this medication should be discontinued and replaced with alternative forms of anticoagulation. *Pseudomonas* bacteremia may cause ecthyma gangrenosum, which may have a necrotic plaque, typically in neutropenic patients. This patient was treated with hyperbaric oxygen, IV thiosulfate, and discontinuation of warfarin with slow resolution of the ulceration.

VI-16. **The answer is D.** *(Chap. 306)* Hypotension is the most common acute complication of hemodialysis, particularly among patients with diabetes mellitus. Numerous factors appear to increase the risk of hypotension, including excessive ultrafiltration with inadequate compensatory vascular filling, impaired vasoactive or autonomic responses, osmolar shifts, overzealous use of antihypertensive agents, and reduced cardiac reserve. Hypotension during dialysis can frequently be prevented by careful evaluation of the dry weight and by ultrafiltration modeling, such that more fluid is removed at the beginning rather than the end of the dialysis procedure. Excessively rapid fluid removal (>13 mL/kg per hour) should be avoided, as rapid fluid removal has been associated with adverse outcomes, including cardiovascular deaths. Additional maneuvers to prevent intradialytic hypotension include the performance of sequential ultrafiltration followed by dialysis, cooling of the dialysate during dialysis treatment, and avoiding heavy meals during dialysis. Muscle cramps during dialysis are also a common complication. The etiology of dialysis-associated cramps remains obscure. Changes in muscle perfusion because of excessively rapid volume removal or targeted removal below the patient's estimated dry weight often precipitate dialysis-associated cramps. Strategies that may be used to prevent cramps include reducing volume removal during dialysis, ultrafiltration profiling, and the use of sodium modeling. Anaphylactoid reactions to the dialyzer, particularly on its first use, have been reported most frequently with the bioincompatible cellulosic-containing membranes. Dialyzer reactions can be divided into two types, A and B. Type A reactions are attributed to an IgE-mediated intermediate hypersensitivity reaction to ethylene oxide used in the sterilization of new dialyzers. This reaction typically occurs soon after the initiation of a treatment (within the first few minutes) and can progress to full-blown anaphylaxis if the therapy is not promptly discontinued. The type B reaction consists of a symptom complex of nonspecific chest and back pain, which appears to result from complement activation and cytokine release. These symptoms typically occur several minutes into the dialysis run and typically resolve over time with continued dialysis.

VI-17. **The answer is E.** *(Chap. 306)* Peritoneal dialysis is associated with a variety of metabolic complications. Albumin and other proteins can be lost across the peritoneal membrane in concert with the loss of metabolic wastes. Hypoproteinemia obligates a higher dietary protein intake to maintain nitrogen balance. Hyperglycemia and weight gain are also common complications of peritoneal dialysis. Several hundred calories in the form of dextrose are absorbed each day, depending on the concentration of dextrose employed. Patients receiving peritoneal dialysis, particularly those with diabetes mellitus, are prone to other complications of insulin resistance, including hypertriglyceridemia. On the positive side, the continuous nature of peritoneal dialysis usually allows for a more liberal diet, due to continuous removal of potassium and phosphorus—two major dietary components whose accumulation can be hazardous in end-stage renal disease.

VI-18. **The answer is B.** *(Chap. 306)* The commonly accepted criteria for initiating patients on maintenance dialysis include the presence of uremic symptoms, the presence of hyperkalemia unresponsive to conservative management, persistent extracellular volume expansion despite diuretics, acidosis refractory to medical therapy, bleeding diathesis, or a creatinine clearance or estimated glomerular filtration rate below 10 mL/min/1.73 m^2. Single blood urea nitrogen or creatinine values alone are inadequate to initiate maintenance dialysis.

VI-19. **The answer is E.** *(Chap. 306)* The major complication of peritoneal dialysis therapy is peritonitis, although other complications include catheter-associated nonperitonitis infections, weight gain, metabolic derangements, and residual uremia. Peritonitis is usually a result of a failure of sterile technique during the exchange procedure. Transvisceral infection from the bowel is much less common. Because of the high dextrose used in dialysate, there is a conducive environment for the development of bacterial infection. This can be diagnosed by the presence of >100/μL leukocytes with >50% polymorphonuclear cells on microscopy. Cloudy dialysate and abdominal pain are the most common symptoms. The most commonly isolated bacteria are skin flora such as *Staphylococcus*. Gram-negative organisms, fungi, and mycobacteria have also been described. A Cochrane review (Wiggins KJ et al: *Cochrane Database Syst Rev* 1:CD005284, 2008) concluded that intraperitoneal administration of antibiotics was more effective than IV administration and that adjunctive treatment with urokinase or peritoneal lavage offers no advantage. Intraperitoneal vancomycin is common initial empiric therapy. In cases where peritonitis is due to hydrophilic gram-negative rods (e.g., *Pseudomonas* spp.) or yeast, antimicrobial therapy is usually not sufficient, and catheter removal is required to ensure complete eradication of infection.

VI-20. **The answer is C.** *(Chap. 306)* The most common cause of mortality in patients with end-stage renal disease is cardiovascular disease (stroke and myocardial infarction). Although the underlying mechanisms driving this association are under active investigation, the shared risk factors of diabetes, hypertension, and dyslipidemia, in addition to specific risks such as increased inflammation, hyperhomocysteinemia, anemia, and altered vascular function, are thought to play an important role. Inefficient or inadequate dialysis is a risk for patients with difficult vascular access or poor adherence to therapy. Patients receiving hemodialysis are at risk and often develop neurologic, hematologic, and infectious complications. Nevertheless, the biggest risk to survival in these patients is also the most common cause of death in the general population.

VI-21. **The answer is A.** *(Chap. 306)* The potassium concentration of dialysate is usually 2.5 mEq/L but may be varied depending on the predialysis serum potassium. This patient may need a lower dialysate potassium concentration. Sodium modeling is an adjustment of the dialysate sodium that may lessen the incidence of hypotension at the end of a dialysis session. Aldosterone defects, if present, are not likely to play a role in this patient since his kidneys are not being perfused. Therefore, nephrectomy is not likely to control his potassium. Similarly, since the patient is likely anuric, there is no efficacy in using loop diuretics to effect kaliuresis. This patient has no approved indications for implantation of a defibrillator.

VI-22. **The answer is C.** *(Chap. 307)* Mycophenolate mofetil or mycophenolate sodium, both of which are metabolized to mycophenolic acid, is now used for maintenance immunosuppression after renal transplant in place of azathioprine in most centers (Table IV-22). It inhibits purine synthesis via inosine monophosphate dehydrogenase. It has a similar mode of action as azathioprine and a mild degree of gastrointestinal toxicity but produces less bone marrow suppression. Its advantage is its increased potency in preventing or reversing rejection. Belatacept is a fusion protein that binds costimulatory ligands (CD80 and CD86) present on antigen presenting cells, interrupting their binding to CD28 on T cells. This inhibition leads to T-cell anergy and apoptosis. Cyclosporine is a fungal peptide with potent immunosuppressive activity. It acts on the calcineurin pathway to block transcription of mRNA for interleukin (IL)-2 and other proinflammatory cytokines, inhibiting T-cell proliferation. Among its toxic effects (nephrotoxicity, hepatotoxicity, hirsutism, tremor, gingival hyperplasia, and diabetes), only nephrotoxicity presents a serious management problem and is further discussed below. Tacrolimus (previously called FK506) is a fungal macrolide that has the same mode of action as cyclosporine as well as a similar side effect profile; it does not, however, produce hirsutism or gingival hyperplasia. Sirolimus (previously called rapamycin) is another fungal macrolide but has a different mode of action; i.e., it inhibits T-cell growth factor signaling pathways, preventing the response to IL-2 and other cytokines.

TABLE VI-22 Maintenance Immunosuppressive Drugs

Agent	Pharmacology	Mechanisms	Side effects
Glucocorticoids	Increased bioavailability with hypoalbuminemia and liver disease; prednisone/prednisolone generally used	Binds cytosolic receptors and heat shock proteins Blocks transcription of IL-1, -2, -3, and -6; TNF-α; and IFN-γ	Hypertension, glucose intolerance, dyslipidemia, osteoporosis
Cyclosporine (CsA)	Lipid-soluble polypeptide, variable absorption, microemulsion more predictable	Trimolecular complex with cyclophilin and calcineurin → block in cytokine (e.g., IL-2) production; however, stimulates TGF-β production	Nephrotoxicity, hypertension, dyslipidemia, glucose intolerance, hirsutism/hyperplasia of gums
Tacrolimus	Macrolide, well absorbed	Trimolecular complex with FKBP-12 and calcineurin → block in cytokine (e.g., IL-2) production; may stimulate TGF-β production	Similar to CsA, but hirsutism/hyperplasia of gums unusual, and diabetes more likely
Azathioprine	Mercaptopurine analogue	Hepatic metabolites inhibit purine synthesis	Marrow suppression (WBC > RBC > platelets)
Mycophenolate mofetil/sodium	Metabolized to mycophenolic acid	Inhibits purine synthesis via inosine monophosphate dehydrogenase	Diarrhea/cramps; dose-related liver and marrow suppression is uncommon
Sirolimus/everolimus	Macrolide, poor oral bioavailability	Complexes with FKBP-12 and then blocks p70 S6 kinase in the IL-2 receptor pathway for proliferation	Hyperlipidemia, thrombocytopenia
Belatacept	Fusion protein, IV injections	Binds CD80 and CD86, prevents CD28 binding and T-cell activation	Posttransplant lymphoproliferative disease

Abbreviations: FKBP-12, FK506 binding protein-12; IFN, interferon; IL, interleukin; RBC, red blood cells; TGF, transforming growth factor; TNF, tumor necrosis factor; WBC, white blood cells.

VI-23. The answer is E. *(Chap. 307)* The number of patients with end-stage renal disease has been increasing every year, and it is always greater than the number of available donors. As the number of patients with end-stage kidney disease increases, the demand for kidney transplantations continues to increase. In 2011, there were 55,371 active adult candidates on the waiting list, and less than 18,000 patients were transplanted. This imbalance is set to worsen over the coming years with the predicted increased rates of obesity and diabetes worldwide. In an attempt to increase utilization of deceased-donor kidneys and reduce discard rates of organs, criteria for the use of so-called expanded criteria donor (ECD) kidneys and kidneys from donors after cardiac death have been developed. ECD kidneys are usually used for older patients who are expected to fare less well on dialysis.

At the 1-year mark, graft survival is higher for living-donor recipients, most likely because those grafts are not subject to as much ischemic injury (Table VI-23). At 5 and 10 years, however, there is a steeper decline in survival of those with deceased-donor kidneys. Among the few absolute immunologic contraindications to transplantation is the presence of antibodies against the donor kidney at the time of the anticipated transplantation that can cause hyperacute rejection. Those harmful antibodies include natural antibodies against the ABO blood group antigens and antibodies against human leukocyte antigen class I (A, B, C) or class II (DR) antigens. These antibodies are routinely excluded by proper screening of the candidate's ABO compatibility and direct cytotoxic cross-matching of candidate serum with lymphocytes of the donor.

TABLE VI-23 Mean Rates of Graft and Patient Survival for Kidneys Transplanted in the United States from 1998 to 2008[a]

	1-Year Follow-Up		5-Year Follow-Up		10-Year Follow-Up	
	Grafts (%)	Patients (%)	Grafts (%)	Patients (%)	Grafts (%)	Patients (%)
Deceased donor	92	96	72	84	46	64
Living donor	96	99	81	91	59	77

[a] All patients transplanted are included, and the follow-up unadjusted survival data from the 1-, 5-, and 10-year periods are presented to show the attrition rates over time within the two types of organ donors.

Source: Data from Summary Tables, 2009 Annual Reports, Scientific Registry of Transplant Recipients.

VI-24. The answer is B. *(Chap. 308)* Proteinuria in frank diabetic nephropathy can be variable, ranging from 500 mg to 25 g per 24 hours, and it is often associated with nephrotic syndrome. The proteinuria is not typically associated with red blood cell casts. More than 90% of patients with type 1 diabetes and nephropathy have diabetic retinopathy, so the absence of retinopathy in type 1 patients with proteinuria should prompt consideration of a diagnosis other than diabetic nephropathy; only 60% of patients with type 2 diabetes with nephropathy have diabetic retinopathy. Also, characteristically, patients with advanced diabetic nephropathy have normal to enlarged kidneys, in contrast to many other glomerular diseases where kidney size is usually decreased. After the onset of proteinuria, renal function inexorably declines, with 50% of patients reaching renal failure over another 5–10 years; thus, from the earliest stages of microalbuminuria, it usually takes 10–20 years to reach end-stage renal disease.

VI-25. The answer is E. *(Chap. 308)* Membranous glomerulonephritis (MGN), or idiopathic membranous nephropathy (IMN) as it is sometimes called, accounts for ~20% of cases of nephrotic syndrome in adults, with a peak incidence between the ages of 30 and 50 years and a male to female ratio of 2:1. IMN is rare in childhood and the most common cause of nephrotic syndrome in the elderly. In 20–30% of cases, MGN is secondary and is associated with a malignancy (solid tumors of the breast, lung, colon); infection (hepatitis B, syphilis, malaria, schistosomiasis); and rheumatologic disorders like lupus, rheumatoid arthritis, IgG4 diseases, or drug exposure (Table VI-25). Drugs causing MGN include gold, mercury, penicillamine, nonsteroidal anti-inflammatory drugs, and probenecid.

TABLE VI-25 Membranous Glomerulonephritis

Primary/idiopathic membranous glomerulonephritis
Secondary membranous glomerulonephritis
Infection: Hepatitis B and C, syphilis, malaria, schistosomiasis, leprosy, filariasis
Cancer: Breast, colon, lung, stomach, kidney, esophagus, neuroblastoma
Drugs: Gold, mercury, penicillamine, nonsteroidal anti-inflammatory agents, probenecid
Autoimmune diseases: Systemic lupus erythematosus, rheumatoid arthritis, primary biliary cirrhosis, dermatitis herpetiformis, bullous pemphigoid, myasthenia gravis, Sjögren syndrome, Hashimoto thyroiditis
Other systemic diseases: Fanconi syndrome, sickle cell anemia, diabetes, Crohn disease, sarcoidosis, Guillain-Barré syndrome, Weber-Christian disease, angiofollicular lymph node hyperplasia

VI-26. The answer is A. *(Chap. 308)* Thrombotic thrombocytopenic purpura (TTP) and hemolytic-uremic syndrome (HUS) represent a spectrum of thrombotic microangiopathies. TTP and HUS share the general features of idiopathic thrombocytopenic purpura, microangiopathic hemolytic anemia, fever, renal failure, and neurologic disturbances. Schistocytes, not spherocytes, are typical on peripheral smear. When patients, particularly children, have more evidence of renal injury, their condition tends to be called HUS. In adults with neurologic disease, it is considered to be TTP. In adults there is often a mixture of both, which is why they are often referred to as having TTP/HUS. In familial cases of adult TTP/HUS, there is a genetic deficiency of the ADAMTS13 metalloprotease that cleaves large multimers of von Willebrand factor. When ADAMTS13 is absent, these large multimers cause platelet clumping and intravascular hemolysis. In the setting of intravascular hemolysis an elevated lactate hydrogenase is usually seen as well as schistocytes on peripheral blood smear. An antibody to ADAMTS13 is found in many sporadic cases of adult TTP/HUS, but not all; many patients also have antibodies to the thrombospondin receptor on selected endothelial cells in small vessels or increased levels of plasminogen-activator inhibitor 1. Patients can be tested for ADAMTS13 activity and, if low, the presence of antibodies to ADAMTS13 distinguishes the deficiency from the immune-mediated disease. Antibodies to red blood cells (positive direct coombs test) are not typically seen in TTP. Anti-glomerular basement membrane antibodies are seen in Goodpasture syndrome, which presents with acute glomerulonephritis and alveolar hemorrhage.

VI-27. The answer is C. *(Chap. 308)* The hallmark of glomerular renal disease is microscopic hematuria and proteinuria (Table VI-27). IgA nephropathy and sickle cell disease are the exception to this, when gross hematuria may be present. Proteinuria may be

TABLE VI-27 Patterns of Clinical Glomerulonephritis

Glomerular Syndromes	Proteinuria	Hematuria	Vascular Injury
Acute Nephritic Syndromes			
Post-streptococcal glomerulonephritis[a]	+/++	++/+++	–
Subacute bacterial endocarditis[a]	+/++	++	–
Lupus nephritis[a]	+/++	++/+++	+
Anti-GBM disease[a]	++	++/+++	–
IgA nephropathy[a]	+/++	+++[c]	–
ANCA small-vessel vasculitis[a]			
Granulomatosis with polyangiitis (Wegener's)	+/++	++/+++	++++
Microscopic polyangiitis	+/++	++/+++	++++
Churg-Strauss syndrome	+/++	++/+++	++++
Henoch-Schönlein purpura[a]	+/++	++/+++	++++
Cryoglobulinemia[a]	+/++	++/+++	++++
Membranoproliferative glomerulonephritis[a]	++	++/+++	–
C_3 Glomerulopathies	++	++/+++	-
Mesangial proliferative glomerulonephritis	+	+/++	–
Pulmonary-Renal Syndromes			
Goodpasture syndrome[a]	++	++/+++	–
ANCA small-vessel vasculitis[a]			
Granulomatosis with polyangiitis (Wegener's)	+/++	++/+++	++++
Microscopic polyangiitis	+/++	++/+++	++++
Churg-Strauss syndrome	+/++	++/+++	++++
Henoch-Schönlein purpura[a]	+/++	++/+++	++++
Cryoglobulinemia[a]	+/++	++/+++	++++
Nephrotic Syndromes			
Minimal change disease	++++	–	–
Focal segmental glomerulosclerosis	+++/++++	+	–
Membranous glomerulonephritis	++++	+	–
Diabetic nephropathy	++/++++	–/+	–
AL and AA amyloidosis	+++/++++	+	+/++
Light-chain deposition disease	+++	+	–
Fibrillary-immunotactoid disease	+++/++++	+	+
Fabry disease	+	+	–
Basement Membrane Syndromes			
Anti-GBM disease[a]	++	++/+++	–
Alport syndrome	++	++	–
Thin basement membrane disease	+	++	–
Nail-patella syndrome	++/+++	++	–
Glomerular Vascular Syndromes			
Atherosclerotic nephropathy	+	+	+++
Hypertensive nephropathy[b]	+/++	+/++	++
Cholesterol emboli	+/++	++	+++
Sickle cell disease	+/++	+++[c]	+++
Thrombotic microangiopathies	++	++	+++
Antiphospholipid syndrome	++	++	+++
ANCA small-vessel vasculitis[a]			
Granulomatosis with polyangiitis (Wegener's)	+/++	++/+++	++++
Microscopic polyangiitis	+/++	++/+++	++++
Churg-Strauss syndrome	+++	++/+++	++++
Henoch-Schönlein purpura[a]	+/++	++/+++	++++
Cryoglobulinemia[a]	+/++	++/+++	++++
AL and AA amyloidosis	+++/++++	+	+/++

(continued)

TABLE VI-27 Patterns of Clinical Glomerulonephritis (*Continued*)

Glomerular Syndromes	Proteinuria	Hematuria	Vascular Injury
Infectious Disease–Associated Syndromes			
Post-streptococcal glomerulonephritis[a]	+/++	++/+++	–
Subacute bacterial endocarditis[a]	+/++	++	–
HIV	+++	+/++	–
Hepatitis B and C	+++	+/++	–
Syphilis	+++	+	–
Leprosy	+++	+	–
Malaria	+++	+/++	–
Schistosomiasis	+++	+/++	–

[a] Can present as rapidly progressive glomerulonephritis (RPGN); sometimes called crescentic glomerulonephritis.

[b] Can present as a malignant hypertensive crisis producing an aggressive fibrinoid necrosis in arterioles and small arteries with microangiopathic hemolytic anemia.

[c] Can present with gross hematuria.

Abbreviations: AA, amyloid A; AL, amyloid L; ANCA, antineutrophil cytoplasmic antibodies; GBM, glomerular basement membrane.

heavy (>3 g per 24 hours) or lighter with microalbuminuria (30–300 mg per 24 hours) depending on the underlying disease or site of the immune lesion. Patients with post-streptococcal glomerulonephritis often have pyuria, but cultures are not expected to be positive because the infection is usually a skin or mucosal infection, and it is the immune reaction that drives the renal lesion.

VI-28. The answer is A. *(Chap. 308)* Focal segmental glomerulosclerosis (FSGS) refers to a pattern of renal injury characterized by segmental glomerular scars that involve some but not all glomeruli; the clinical findings of FSGS largely manifest as proteinuria. When the secondary causes of FSGS are eliminated, the remaining patients are considered to have primary FSGS. Secondary causes of FSGS include viral infection (HIV, hepatitis B, parvovirus), hypertensive nephropathy, reflux nephropathy, cholesterol emboli, drugs (heroin, analgesics, pamidronate), oligomeganephronia, renal dysgenesis, Alport syndrome, sickle cell disease, lymphoma, radiation nephritis, and a number of familial podocytopathies. The incidence of FSGS is increasing, and it now represents up to one-third of cases of nephrotic syndrome in adults and one-half of cases of nephrotic syndrome in African Americans, in whom it is seen more commonly. FSGS can present with hematuria, hypertension, any level of proteinuria, or renal insufficiency. Nephrotic-range proteinuria, African American race, and renal insufficiency are associated with a poor outcome, with 50% of patients reaching renal failure in 6–8 years. FSGS rarely remits spontaneously, but treatment-induced remission of proteinuria significantly improves prognosis. Treatment of patients with primary FSGS should include inhibitors of the renin-angiotensin system. The treatment of secondary FSGS typically involves treating the underlying cause and controlling proteinuria. There is no role for steroids or other immunosuppressive agents in secondary FSGS. Hypertensive nephrosclerosis exhibits more prominent vascular changes and patchy, ischemic, totally sclerosed glomeruli. In addition, nephrosclerosis seldom is associated with nephrotic-range proteinuria. Minimal change disease usually is associated with symptomatic edema and normal-appearing glomeruli as demonstrated on light microscopy. This patient's presentation is consistent with that of membranous nephropathy, but the biopsy is not. With membranous glomerulonephritis, all glomeruli are uniformly involved with subepithelial dense deposits. There are no features of crescentic glomerulonephritis present. The characteristic pattern of focal (not all glomeruli) and segmental (not the entire glomerulus) glomerular scarring is shown in the figure. The history and laboratory features are also consistent with this lesion: some associated hypertension, diminution in creatinine clearance, and a relatively inactive urine sediment. The "nephropathy of obesity" may be associated with this lesion secondary to hyperfiltration; this condition may be more likely to occur in obese patients with hypoxemia, obstructive sleep apnea, and right-sided heart failure.

VI-29. The answer is E. *(Chap. 309)* Tuberous sclerosis (TS) is a rare autosomal dominant syndrome caused by mutations in one of two genes, *TSC1*, encoding hamartin, or, *TSC2*, encoding tuberin. Published estimates of prevalence vary widely, but it certainly occurs in <1:5000 births. Kidney cysts are a frequent feature of this condition, as are two other abnormalities of kidney growth, renal cell carcinoma, and renal angiomyolipomas. TS is a syndrome affecting multiple organ systems. Other features of TS include benign growths in the nervous system, eyes, heart, lung, liver, and the skin. Von Hippel-Lindau disease (VHL) is an inherited cancer syndrome with renal manifestations. VHL is an autosomal dominant condition caused by mutations in the VHL tumor-suppressor gene. VHL is localized to the primary cilia and is necessary for the formation of primary cilia. Like many autosomal dominant cancer syndromes, VHL is recessive at the cellular level: a somatic mutation in the second VHL allele leads to loss of VHL in the cell and abnormal growth. Kidney manifestations of VHL include multiple bilateral kidney cysts and renal cell carcinomas. Medullary sponge kidney (MSK) is often grouped together with inherited disorders of the kidney affecting tubule growth and development, although it is usually a sporadic finding rather than an inherited phenotype. MSK is caused by developmental malformation and cystic dilatation of the renal collecting ducts. The medullary cysts seen in this entity can be quite variable in size. MSK is usually a benign entity. Neurofibromatosis type 1 is a genetic disease that is characterized by café au lait macules and cutaneous neurofibromas. Patients with neurofibromatosis type 1 may also develop optic gliomas, iris hamartomas, destructive bony lesions, or sarcomas.

VI-30. **The answer is E.** *(Chap. 309)* Patients with autosomal dominant polycystic kidney disease have a two- to fourfold increased risk of subarachnoid or cerebral hemorrhage compared with the general population. Hemorrhage tends to occur before age 50 in patients with a family history of intracranial hemorrhage, with a personal history of intracranial hemorrhage, with aneurysms >10 mm, or with uncontrolled hypertension.

VI-31. **The answer is C.** *(Chap. 309)* The patient presents with hypokalemia and hypochloremic metabolic alkalosis in the absence of hypertension. This is most commonly due to surreptitious vomiting or diuretic abuse, but in this case, the urine diuretic screen was negative. In patients with surreptitious vomiting, urine chloride levels are low to preserve intravascular volume, and this was not present in this patient. Bartter syndrome and Gitelman syndrome have hypokalemia and hypochloremic metabolic alkalosis with inappropriately elevated urine chloride levels. Gitelman syndrome is less severe and presents later in life than Bartter syndrome, which is commonly found in childhood due to failure to thrive. Additionally, Gitelman syndrome has more prominent fatigue and muscle cramping. Most forms of Bartter syndrome also have associated hypomagnesemia and hypocalciuria. Patients with type 1 pseudohypoaldosteronism have severe renal salt wasting and hyperkalemia. Liddle syndrome presents with apparent aldosterone excess with severe hypertension, hypokalemia, and metabolic alkalosis.

VI-32. **The answer is C.** *(Chap. 310)* Reflux nephropathy is the consequence of vesicoureteral reflux (VUR) or other urologic anomalies in early childhood. VUR stems from abnormal retrograde urine flow from the bladder into one or both ureters and kidneys because of mislocated and incompetent ureterovesical valves. Although high-pressure sterile reflux may impair normal growth of the kidneys, when coupled with recurrent urinary tract infections (UTIs) in early childhood, the result is patchy interstitial scarring and tubular atrophy. Loss of functioning nephrons leads to hypertrophy of the remnant glomeruli and eventual secondary focal segmental glomerulosclerosis. Reflux nephropathy often goes unnoticed until early adulthood when chronic kidney disease is detected during routine evaluation or during pregnancy. Affected adults are frequently asymptomatic, but may give a history of prolonged bed-wetting or recurrent UTIs during childhood, and exhibit variable renal insufficiency, hypertension, mild to moderate proteinuria, and unremarkable urine sediment. When both kidneys are affected, the disease often progresses inexorably over several years to ESRD, despite the absence of ongoing urinary infections or reflux. A single affected kidney may go undetected, except for the presence of hypertension. Renal ultrasound in adults characteristically shows asymmetric small kidneys with irregular outlines, thinned cortices, and regions of compensatory hypertrophy. The patient has not been exposed to any medications that typically cause allergic interstitial nephritis. There are no indications of Sjögren syndrome or sickle cell by history or laboratory findings. IgG4 disease is typically present in older men and can cause interstitial nephritis.

VI-33. **The answer is B.** *(Chap. 310)* Although biopsy-proven acute interstitial nephritis (AIN) accounts for no more than ~15% of cases of unexplained acute renal failure, this is likely a substantial underestimate of the true incidence (Table VI-33). This is because potentially offending medications are more often identified and empirically discontinued in a patient noted to have a rising serum creatinine, without the benefit of a renal biopsy to establish the diagnosis of AIN. The classic presentation of AIN, namely, fever, rash, peripheral

TABLE VI-33 Classification of the Causes of Tubulointerstitial Diseases of the Kidney

Acute Tubulointerstitial Disorders
Acute Interstitial Nephritis
Therapeutic agents • Antibiotics (β-lactams, sulfonamides, quinolones, vancomycin, erythromycin, linezolid, minocycline, rifampin, ethambutol, acyclovir) • Nonsteroidal anti-inflammatory drugs, COX-2 inhibitors • Diuretics (rarely thiazides, loop diuretics, triamterene) • Anticonvulsants (phenytoin, valproate, carbamazepine, phenobarbital) • Miscellaneous (proton pump inhibitors, H_2 blockers, captopril, mesalazine, indinavir, allopurinol, lenalidomide) Infection • Bacteria (*Streptococcus, Staphylococcus, Legionella, Salmonella, Brucella, Yersinia, Corynebacterium diphtheriae*) • Viruses (EBV, CMV, hantavirus, polyomavirus, HIV) • Miscellaneous (*Leptospira, Rickettsia, Mycoplasma, Histoplasma*) Autoimmune • Tubulointerstitial nephritis with uveitis • Sjögren syndrome • Systemic lupus erythematosus • Granulomatous interstitial nephritis • IgG4-related systemic disease • Idiopathic autoimmune interstitial nephritis Acute obstructive disorders • Light chain cast nephropathy (“myeloma kidney”) • Acute phosphate nephropathy • Acute urate nephropathy
Chronic Tubulointerstitial Disorders
• Vesicoureteral reflux/reflux nephropathy • Sickle cell disease • Chronic exposure to toxins or therapeutic agents • Analgesics, especially those containing phenacetin • Lithium • Heavy metals (lead, cadmium) • Aristolochic acid (Chinese herbal and Balkan endemic nephropathies) • Calcineurin inhibitors (cyclosporine, tacrolimus)
Metabolic Disturbances
• Hypercalcemia and/or nephrocalcinosis • Hyperuricemia • Prolonged hypokalemia • Hyperoxaluria • Cystinosis (see Chap. 309 in HPIM 20)
Cystic and Hereditary Disorders (see Chap. 309 in HPIM 20)
• Polycystic kidney disease • Nephronophthisis • Adult medullary cystic disease • Medullary sponge kidney
Miscellaneous
• Aging • Chronic glomerulonephritis • Chronic urinary tract obstruction • Ischemia and vascular disease • Radiation nephritis (rare)

Abbreviations: CMV, cytomegalovirus; COX, cyclooxygenase; EBV, Epstein-Barr virus.

eosinophilia, and oliguric renal failure occurring after 7–10 days of treatment with methicillin or another β-lactam antibiotic, is the exception rather than the rule. More often, patients are found incidentally to have a rising serum creatinine or present with symptoms attributable to acute renal failure. All of the listed drugs except hydromorphone have been associated with AIN. Opiates are not known to cause AIN.

VI-34. The answer is B. *(Chaps. 49 and 310)* This patient has a normal anion gap metabolic acidosis (anion gap, 12). The calculated urine anion gap ($Na^+ + K^+ - Cl^-$) is +3; thus, the acidosis is unlikely to be due to gastrointestinal bicarbonate loss. In this patient, the diagnosis is type I renal tubular acidosis (RTA), or distal RTA. This is a disorder in which the distal nephron does not lower pH normally. It is associated with a urine pH >5.5, hypokalemia, and lack of bicarbonaturia. Sjögren syndrome is one of the autoimmune diseases (along with systemic lupus erythematosus, granulomatous interstitial nephritis, IgG4-related systemic disease, and idiopathic autoimmune interstitial nephritis) that may be associated with acute interstitial nephritis and tubular dysfunction. Sjögren-associated type I RTA may be associated with calcium phosphate stones and nephrocalcinosis. Type II RTA, or proximal RTA, includes a pH <5.5, hypokalemia, a positive urine anion gap, bicarbonaturia, hypophosphatemia, and hypercalciuria. This condition results from defective resorption of bicarbonate. Type III RTA is rare and most commonly is seen in children. Type IV RTA is also referred to as hyperkalemic distal RTA. Hyporeninemic hypoaldosteronism is the most common cause of type IV RTA and is usually associated with diabetic nephropathy.

VI-35. The answer is A. *(Chap. 310)* Acute interstitial nephritis is a common cause of both acute and chronic kidney dysfunction. Many causes of interstitial nephritis are successfully treated with glucocorticoids with improved rates of long-term renal recovery, including Sjögren syndrome, sarcoidosis, systemic lupus erythematosus, adult tubulointerstitial nephritis with uveitis, and idiopathic or other granulomatous interstitial nephritis (Table VI-35). In patients with gradually progressive disease or fibrosis on biopsy, the benefit is less clear. Additionally, allergic interstitial nephritis recovery may be accelerated with glucocorticoid therapy, but long-term renal recovery is not proven to be improved. Postinfectious interstitial nephritis has been associated with many bacterial and viral pathogens but generally resolves with treatment of the underlying condition.

TABLE VI-35 Indications for Corticosteroids and Immunosuppressives in Interstitial Nephritis

Absolute Indications
• Sjögren syndrome • Sarcoidosis • SLE interstitial nephritis • Adults with TINU • Idiopathic and other granulomatous interstitial nephritis
Relative Indications
• Drug-induced or idiopathic AIN with: Rapid progression of renal failure Diffuse infiltrates on biopsy Impending need for dialysis Delayed recovery • Children with TINU • Postinfectious AIN with delayed recovery (?)

Abbreviations: AIN, acute interstitial nephritis; SLE, systemic lupus erythematosus; TINU, tubulointerstitial nephritis with uveitis.
Source: Data from Reddy S, Salant DJ: Treatment of acute interstitial nephritis. *Ren Fail* 20:829, 1998.

VI-36. The answer is E. *(Chap. 310)* Allergic interstitial nephritis is a common cause of unexplained acute renal failure. This is generally a clinical diagnosis with acute renal failure in the context of exposure to a potential offending agent (often nonsteroidal anti-inflammatory drugs, antibiotics, anticonvulsants, and proton pump inhibitors) and improvement in renal function with withdrawal of the agent. Peripheral blood eosinophilia supports the diagnosis but is rarely found. Urine microscopy often shows white blood cell casts and hematuria, but these are not specific findings. Urine eosinophils are neither sensitive nor specific for allergic interstitial nephritis. A renal biopsy is generally not required, but may show extensive tubulointerstitial infiltration of white cells including eosinophils. Discontinuation of the offending agent often leads to reversal of the renal injury. However, depending on the duration of exposure and degree of tubular atrophy and interstitial fibrosis that has occurred, the renal damage may not be completely reversible. Glucocorticoid therapy may accelerate renal recovery but does not appear to impact long-term renal survival. It is best reserved for patients with severe renal failure in which dialysis is imminent or if renal function continues to deteriorate despite stopping the offending drug.

VI-37. **The answer is A.** *(Chap. 311)* Atypical hemolytic-uremic syndrome (HUS) or complement-mediated HUS is the result of complement dysregulation. The complement dysregulation can be congenital or acquired. The affected patients often have a low C3 and normal C4 levels characteristic of alternative pathway activation. Factor H deficiency, the most common defect, has been linked to families with atypical HUS (aHUS). Deficiencies in other complement-regulatory proteins, such as factor I, factor B, membrane cofactor protein (CD46), C3, complement factor H–related protein 1 (CFHR1), CFHR3, CFHR5, and thrombomodulin, have also been reported. Finally, an autoimmune variant of aHUS has been discovered. DEAP (deficiency of CFHR plasma proteins and CFH autoantibody–positive) HUS occurs when an autoantibody to factor H is formed. Eculizumab is a monoclonal antibody to C5 that is approved for use in aHUS, which has been shown to abort microangiopathic hemolytic anemia and improve renal function.

VI-38. **The answer is B.** *(Chap. 311)* Scleroderma renal crisis occurs in 12% of patients with diffuse systemic sclerosis but in only 2% of those with limited systemic sclerosis. Scleroderma renal crisis is the most severe manifestation of renal involvement, and it is characterized by accelerated hypertension, a rapid decline in renal function, nephrotic range proteinuria, and hematuria. Retinopathy and encephalopathy may accompany the hypertension. Salt and water retention with microvascular injury can lead to pulmonary edema. Cardiac manifestations, including myocarditis, pericarditis, and arrhythmias, denote an especially poor prognosis. Although microangiopathic hemolytic anemia (MAHA) is present in more than half of patients, coagulopathy is rare. The renal lesion in scleroderma renal crisis is characterized by arcuate artery intimal and medial proliferation with luminal narrowing. This lesion is described as "onion-skinning" and can be accompanied by glomerular collapse due to reduced blood flow. Histologically, scleroderma renal crisis is indistinguishable from malignant hypertension, with which it can coexist. Fibrinoid necrosis and thrombosis are common. Before the availability of angiotensin-converting enzyme (ACE) inhibitors, the mortality rate for scleroderma renal crisis was >90% at 1 month. Introduction of renin-angiotensin system blockade has lowered the mortality rate to 30% at 3 years. Nearly two-thirds of patients with scleroderma renal crisis may require dialysis support, with recovery of renal function in 50% (median time, 1 year). Treatment with ACE inhibition is the first-line therapy unless contraindicated. The goal of therapy is to reduce systolic and diastolic blood pressure by 20 mmHg and 10 mmHg, respectively, every 24 hours until blood pressure is normal. Additional antihypertensive therapy, such as calcium channel blockers like amlodipine, may be given once the dose of drug for ACE inhibition is maximized. Both ACE inhibitors and angiotensin II receptor antagonists are effective, although data suggest that treatment with ACE inhibitors is superior. ACE inhibition alone does not prevent scleroderma renal crisis, but it does reduce the impact of hypertension. Eculizumab is used in another cause of MAHA, atypical hemolytic-uremic syndrome, and plasmapheresis is a key treatment for thrombotic thrombocytopenic purpura. There is no role for heparin to treat scleroderma renal crisis.

VI-39. **The answer is C.** *(Chap. 311)* Renal vein thrombosis occurs in 10–15% of patients with nephrotic syndrome accompanying membranous glomerulopathy and oncologic disease. The clinical manifestations can be variable but may be characterized by fever, lumbar tenderness, leukocytosis, and hematuria. Magnetic resonance venography is the most sensitive and specific noninvasive form of imaging to make the diagnosis of renal vein thrombosis. Ultrasound with Doppler is operator dependent and therefore may be less sensitive. Contrast venography is the gold standard for diagnosis, but it exposes the patient to a more invasive procedure and contrast load. Nuclear medicine screening is not performed to make this diagnosis.

VI-40. **The answer is A.** *(Chap. 311)* HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome is a dangerous complication of pregnancy associated with microvascular injury. Occurring in 0.2–0.9% of all pregnancies and in 10–20% of women with severe preeclampsia, this syndrome carries a mortality rate of 7.4–34%. Most commonly developing in the third trimester, 10% of cases occur before week 27, and 30% occur postpartum. Although a strong association exists between HELLP syndrome and preeclampsia, nearly 20% of cases are not preceded by recognized preeclampsia. Risk factors include abnormal placentation, family history, and elevated levels of fetal mRNA for FLT1 (vascular endothelial growth factor receptor 1) and endoglin. Patients with HELLP syndrome have higher levels of inflammatory markers (C-reactive protein, interleukin[IL]-1Ra, and IL-6) and soluble HLA-DR than do those with preeclampsia alone. Renal failure occurs in half of patients with HELLP syndrome, although the etiology is not well understood. Although renal failure is common, the organ that defines this syndrome is the liver. Subcapsular hepatic hematomas sometimes produce spontaneous rupture of the liver and can be life-threatening. Neurologic complications such as cerebral infarction, cerebral and brainstem hemorrhage, and cerebral edema are other potentially life-threatening complications. Many features are shared by HELLP syndrome, atypical HUS (aHUS), and thrombotic thrombocytopenic purpura (TTP). Diagnosis of HELLP syndrome is complicated by the fact that aHUS and TTP also can be triggered by pregnancy. Serum levels of ADAMTS13 activity are reduced (by 30–60%) in HELLP syndrome but not to the levels seen in TTP (<5%). Other markers, such as antithrombin III (decreased in HELLP syndrome but not in TTP) and D-dimer (elevated in HELLP syndrome but not in TTP), may also be useful. HELLP syndrome usually resolves spontaneously after delivery, although some HELLP cases occur postpartum. Glucocorticoids may decrease inflammatory markers, although two randomized controlled trials failed to show a mortality/morbidity benefit. Plasma exchange should be considered if hemolysis is refractory to glucocorticoids and/or delivery, especially if TTP has not been ruled out.

VI-41. **The answer is D.** *(Chap. 312)* Risk factors for calcium oxalate stones include higher urine calcium, higher urine oxalate, and lower urine citrate. Individuals with higher urine calcium excretion tend to absorb a higher percentage of ingested calcium. Nevertheless, dietary calcium restriction is not beneficial and, in fact, is likely to be harmful. In a randomized trial in men with high urine calcium and recurrent calcium oxalate stones, a diet containing 1200 mg of calcium and a low intake of sodium and animal protein significantly reduced subsequent stone formation from that with a low-calcium diet (400 mg/d). A thiazide diuretic, in doses higher than those used to treat hypertension, can substantially lower urine calcium excretion. Several randomized controlled trials have demonstrated that thiazide diuretics, most commonly chlorthalidone, can reduce calcium oxalate stone recurrence by ~50%. A reduction in urine oxalate will in turn reduce the supersaturation of calcium oxalate. In patients with the common form of nephrolithiasis, avoiding high-dose vitamin C supplements is the only known strategy that reduces endogenous oxalate production. Oxalate is a metabolic end product; therefore, any dietary oxalate that is absorbed will be excreted in the urine. Spinach, rhubarb, beer, and chocolate are all rich in oxalate. Aspirin has no known effect on nephrolithiasis.

VI-42. and VI-43. **The answers are D and B, respectively.** *(Chap. 312)* This patient has a typical clinical, laboratory, and radiologic presentation of nephrolithiasis. The CT shows a 10-mm obstructing calculus in the distal left ureter at the level of S1 and another 6-mm stone in the interpolar region of the left kidney. There is also left hydronephrosis and perinephric fat stranding. At present, there are no widely accepted, evidence-based guidelines for the evaluation and treatment of nephrolithiasis. The diagnosis is often made based on the history, physical examination, and urinalysis. Thus, it may not be necessary to wait for radiographic confirmation before treating the symptoms. The diagnosis is confirmed by an appropriate imaging study, preferably helical CT, which is highly sensitive, allows visualization of uric acid stones (traditionally considered "radiolucent"), and is able to avoid radiocontrast. Helical CT detects stones as small as 1 mm that may be missed by other imaging modalities. Typically, helical CT reveals a ureteral stone or evidence of recent passage (e.g., perinephric stranding or hydronephrosis), whereas a plain abdominal radiograph (kidney/ureter/bladder) can miss a stone in the ureter or kidney, even if it is radiopaque, and does not provide information on obstruction. Abdominal ultrasound offers the advantage of avoiding radiation and provides information on hydronephrosis, but it is not as sensitive as CT and images only the kidney and possibly the proximal segment of the ureter; thus, most ureteral stones are not detectable by ultrasound. Urologic intervention, such as cystoscopy, should be postponed unless there is evidence of a urinary tract infection (UTI), a low probability of spontaneous stone passage (e.g., a stone measuring ≥6 mm or an anatomic abnormality), or intractable pain. A ureteral stent may be placed cystoscopically, but this procedure typically requires general anesthesia, and the stent can be quite uncomfortable, may cause gross hematuria, and may increase the risk of UTI. Many patients who experience their first episode of colic seek emergent medical care. Randomized trials have demonstrated that parenterally administered nonsteroidal anti-inflammatory drugs (such as ketorolac) are just as effective as opioids in relieving symptoms and have fewer side effects. Excessive fluid administration has not been shown to be beneficial; therefore, the goal should be to maintain euvolemia. Use of an alpha blocker may increase the rate of spontaneous stone passage.

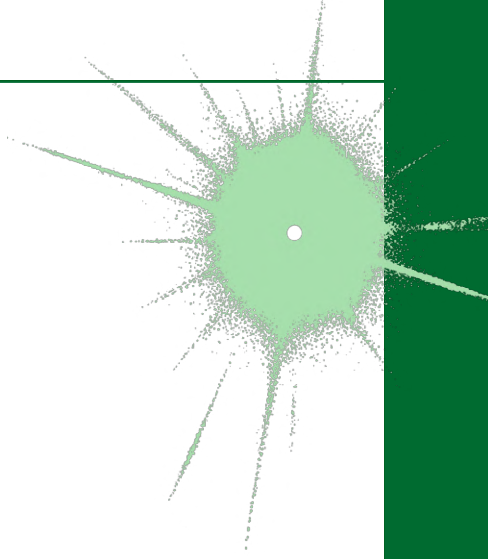
VI-44. **The answer is E.** *(Chap. 313)* Relief of bilateral, but not unilateral, complete renal obstruction commonly results in polyuria, which may be massive and is known as postobstructive diuresis. The urine is usually hypotonic and may contain large amounts of sodium chloride, potassium, phosphate, and magnesium. The natriuresis is due in part to the correction of extracellular volume expansion, the increase in natriuretic factors accumulated during the period of renal failure, and depressed salt and water reabsorption when urine flow is reestablished. The retained urea is excreted with improved glomerular filtration rate, resulting in an osmotic diuresis, which increases the urine volume of electrolyte-free water. The urinary concentrations of sodium and potassium that when added are less than the serum sodium is evidence of electrolyte-free water excretion. In the majority of patients, this diuresis results in the *appropriate* excretion of the excesses of retained salt and water. When extracellular volume and composition return to normal, the diuresis usually abates spontaneously. Occasionally, iatrogenic expansion of extracellular volume is responsible for, or sustains, the diuresis observed in the postobstructive period. Replacement with IV fluids in amounts less than urinary losses usually prevents this complication. More aggressive fluid management is required in the setting of hypovolemia, hypotension, or disturbances in serum electrolyte concentrations. The loss of electrolyte-free water with urea may result in hypernatremia. Measured urinary output and serum and urine sodium, potassium, and osmolal concentrations should guide the use of appropriate IV replacement. Often replacement with 0.45% saline is required. Relief of obstruction may be followed by urinary salt and water losses severe enough to provoke profound dehydration and vascular collapse. In these patients, decreased tubular reabsorptive capacity is probably responsible for the marked diuresis. Appropriate therapy in such patients includes IV administration of salt-containing solutions to replace sodium and volume deficits.

VI-45. **The answer is D.** *(Chap. 313)* Urinary tract obstruction is an important and potentially reversible cause of kidney failure. This patient is at risk for urinary obstruction based on her history of colon cancer. Although recent nonsteroidal anti-inflammatory drug use may be contributing to the rapidity of her kidney damage, routine dosing is less likely to cause acute kidney injury in the absence of pre-existing renal dysfunction. Ultrasound of the kidneys is the best screening test for obstruction. Hydroureter and/or hydronephrosis may be found and suggest presence of obstruction. Although obstruction may be unilateral, it rarely causes clinically significant renal failure in the absence of underlying renal disease. CT of the abdomen is useful after ultrasound to evaluate the site and etiology of obstruction. Postvoid residual is useful if functional causes of obstruction are suspected, such as urinary retention. After the obstruction site is located, retrograde urography with stent placement may be indicated, but only after defining the presence or absence of obstruction.

VI-46. **The answer is C.** *(Chap. 313)* In acute urinary tract obstruction, pain is due to distention of the collecting system or renal capsule. Acutely, there is a compensatory increase in renal blood flow when kidney function is impaired by obstruction, which further exacerbates capsular stretch. Eventually, vasodilatory prostaglandins act to preserve renal function when glomerular filtration rate has decreased. Medullary blood flow decreases as the pressure of the obstruction further inhibits the renal parenchyma from perfusing; however, the ensuing chronic renal destruction may occur without substantial pain. When an obstruction has been relieved, there is a postobstructive diuresis that is mediated by relief of tubular pressure, increased solute load (per nephron), and natriuretic factors. There can be an extreme amount of diuresis, but this is not painful.

SECTION VII

Disorders of the Gastrointestinal System



QUESTIONS

VII-1. All of the following are true about specific functions of the gut EXCEPT:

A. Gastric acid sterilizes the upper gut.
B. Most nutrient absorption occurs in the small intestine.
C. The pancreas secretes bicarbonate, which optimizes the pH in the intestine for enzyme activation.
D. The stomach secretes intrinsic factor which is necessary for vitamin B_{12} absorption.
E. The terminal ileum is primarily responsible for stool dehydration, decreasing volumes from 1000–1500 mL to 100–200mL.

VII-2. All of the following diseases are associated with gastric acid hypersecretion EXCEPT:

A. Duodenal ulcers
B. G-cell hyperplasia
C. Pernicious anemia
D. Retained antrum syndrome
E. Zollinger-Ellison syndrome

VII-3. Which of the following gastrointestinal conditions is characterized by noninflammatory visceral pain?

A. Appendicitis
B. Cholecystitis
C. Inflammatory bowel disease
D. Mesenteric ischemia
E. Peptic ulcer

VII-4. Which of the following statements regarding gastrointestinal symptoms is TRUE?

A. Diarrhea from malabsorption usually improves with fasting, whereas secretory diarrhea persists without oral intake.
B. Sudden awakening from a sound sleep by pain suggests functional rather than organic disease.
C. Symptoms from mechanical obstruction, ischemia, inflammatory bowel disease, and functional bowel disorders are alleviated by meals.
D. Ulcer pain is typically acute in onset.
E. Ulcer symptoms are usually made worse by eating.

VII-5. A 57-year-old female wishes to undergo a screening colonoscopy for colon cancer. She has no family history of colon cancer and currently has no symptoms referable to the gastrointestinal tract. Which of the following statements is true about colonoscopy as a screening test for colon cancer?

A. Barium enema is as sensitive as colonoscopy for detecting colitis.
B. Colonoscopy remains the gold standard for imaging the colonic mucosa.
C. CT colonography has replaced traditional colonoscopy for many younger patients because of its ability to detect serrated polyps with greater sensitivity.
D. Flexible sigmoidoscopy would be as effective as colonoscopy for detecting colon cancer in this patient.
E. The cecum can only be reached in 75% of colonoscopies.

VII-6. Which of the following endoscopic procedures would warrant antibiotic prophylaxis?

A. Endoscopic procedures in patients with prosthetic joints
B. Endoscopic procedures in patients with synthetic vascular grafts
C. Endoscopic ultrasound with fine-needle aspiration in a patient with a lower gastrointestinal tract lesion
D. Endoscopic retrograde cholangiopancreatography with anticipated complete drainage in a patient with biliary obstruction in the absence of cholangitis
E. Percutaneous endoscopic feeding tube placement

VII-7. All of the following are indications for urgent endoscopy for acute upper gastrointestinal bleeding EXCEPT:

A. Bloody nasogastric aspirate that does not clear with large volume lavage
B. Large volume initial bleed
C. Orthostatic hypotension
D. Resting hypotension
E. Severe pain

VII-8. Mr. Tyler, a 45-year-old male with known chronic alcohol use, presents with two episodes of hematemesis. He recently sustained a fall and injured his knee. He has been taking ibuprofen several times a day for the last week for pain control. His initial hemoglobin is 10 g/dL. He receives 2 L of IV fluid and undergoes an urgent upper endoscopy. All of the following are true about his risk of rebleeding without intervention EXCEPT:

A. A clean-based ulcer is associated with a low risk (3–5%) of rebleeding.
B. Adherent clots covering the ulcer base have a 90% risk of rebleeding.
C. Flat pigmented spots covering the ulcer base have a 10% risk of rebleeding.
D. When a fibrin plug is seen protruding from a vessel wall in the base of an ulcer, (so-called sentinel clot or visible vessel), the risk of rebleeding from the ulcer is 40%.
E. When active spurting from an ulcer is seen, there is a 90% risk of ongoing bleeding without therapy.

VII-9. The advantages of endoscopy over barium radiography in the evaluation of dysphagia include all of the following EXCEPT:

A. Ability to assess function and morphology
B. Ability to intervene as well as diagnose
C. Ability to obtain biopsy specimens
D. Increased sensitivity for the detection of abnormalities identified by color, e.g., Barrett metaplasia
E. Increased sensitivity for the detection of mucosal lesions

VII-10. A 47-year-old man is evaluated in the emergency department for chest pain that developed at a restaurant after swallowing a piece of steak. He reports intermittent episodes of meat getting stuck in his lower chest over the past 3 years, but none as severe as this event. He denies food regurgitation outside of these episodes or heartburn symptoms. He is able to swallow liquids without difficulty and has not had any weight loss. Which of the following is the most likely diagnosis?

A. Achalasia
B. Adenocarcinoma of the esophagus
C. Esophageal diverticula
D. Plummer-Vinson syndrome
E. Schatzki ring

VII-11. A 36-year-old woman with AIDS and a CD4 count of 35/μL presents with odynophagia and progressive dysphagia. The patient reports daily fevers and a 20-lb weight loss. The patient has been treated with clotrimazole troches without relief. On physical examination, she is cachectic with a body mass index of 16 and a weight of 86 lb. Her temperature is 38.2°C (100.8°F). She is noted to be orthostatic by blood pressure and pulse. Examination of the oropharynx reveals no evidence of thrush. The patient undergoes esophagogastroduodenoscopy, which reveals serpiginous ulcers in the distal esophagus without vesicles. No yellow plaques are noted. Multiple biopsies are taken that show intranuclear and intracytoplasmic inclusions in large endothelial cells and fibroblasts. What is the best treatment for this patient's esophagitis?

A. Ganciclovir
B. Glucocorticoids
C. Fluconazole
D. Foscarnet
E. Thalidomide

VII-12. A 43-year-old man presents with 6 months of worsening dysphagia and postprandial regurgitation. He reports difficulty and pain with swallowing both liquids and solids; he has no difficulty with the initial components of swallowing but reports pain in the mid-chest region. He frequently regurgitates undigested food 20–60 minutes after eating or drinking. In the past 2 months, he has lost 15 lb. He also has had one episode of presumed pneumonia 4 months ago notable for a right lower lobe infiltrate. He has no significant past medical history, takes no medications, and does not smoke cigarettes. He works as a service

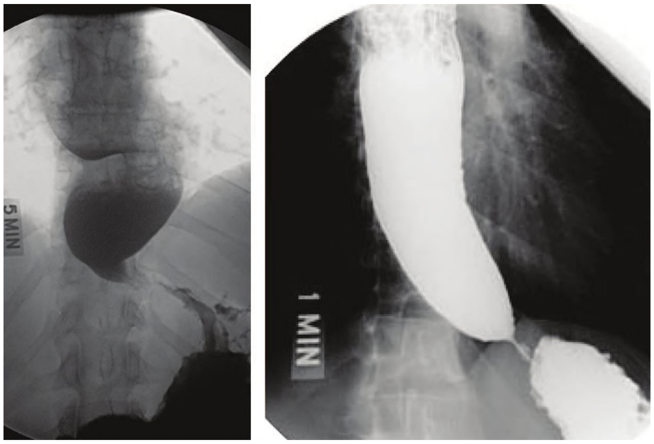


FIGURE VII-12

representative at a major electronics store and has never left the United States. Other than signs of recent weight loss, his physical examination is unremarkable. A barium swallow is performed and shown in Figure VII-12. Which of the following is the most likely cause of his disease?

A. Autoimmune reaction to latent herpes virus
B. Diffuse spasm on smooth muscle
C. Infection by *Trypanosoma cruzi*
D. Malignant growth of columnar epithelial cells
E. Malignant growth squamous epithelial cells

VII-13. A 64-year-old man with a long history of abdominal pain, heartburn, and dyspepsia has an esophagogastroduodenoscopy to evaluate for peptic ulcer disease. No gastric or duodenal ulcers are found, but there are tongues of reddish mucosa extending proximally from the gastroesophageal junction into the esophagus. Biopsies of these areas demonstrate columnar metaplasia. All of the following statements regarding this diagnosis are true EXCEPT:

A. Finding high-grade dysplasia mandates further intervention.
B. High-dose proton pump inhibitor therapy will likely cause regression of the mucosal abnormalities.
C. The incidence of these lesions has increased in the era of potent acid suppression.
D. The patient has a high risk of coexisting cancer.
E. The patient is at significant risk of esophageal adenocarcinoma.

VII-14. A 35-year-old man presents with progressive dysphagia over a 2-month period. He has noted that food has been getting stuck more frequently in the last 2 weeks. He has a history of intermittent gastroesophageal reflux disease for which he takes over-the-counter antacids every few weeks. He has a history of eczema as a child but is not currently requiring treatment. He undergoes an esophagogastroduodenoscopy, which is shown in Figure VII-14A. The biopsy is shown in Figure VII-14B.

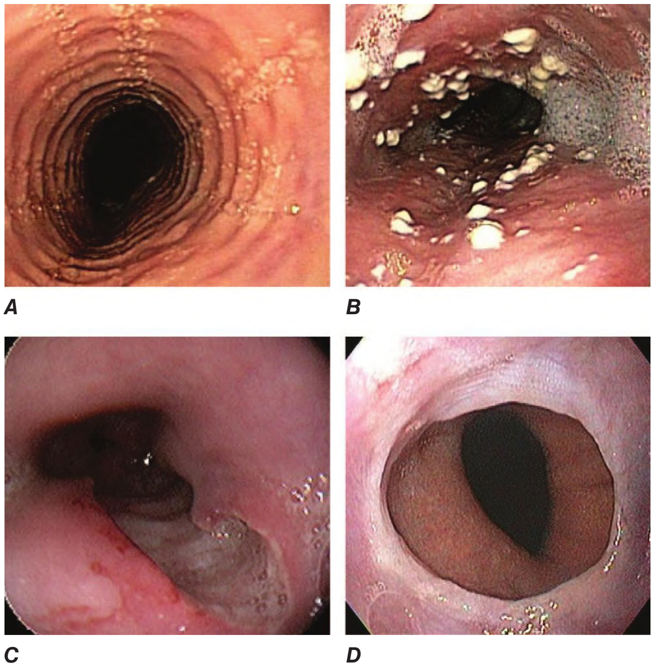


FIGURE VII-14A

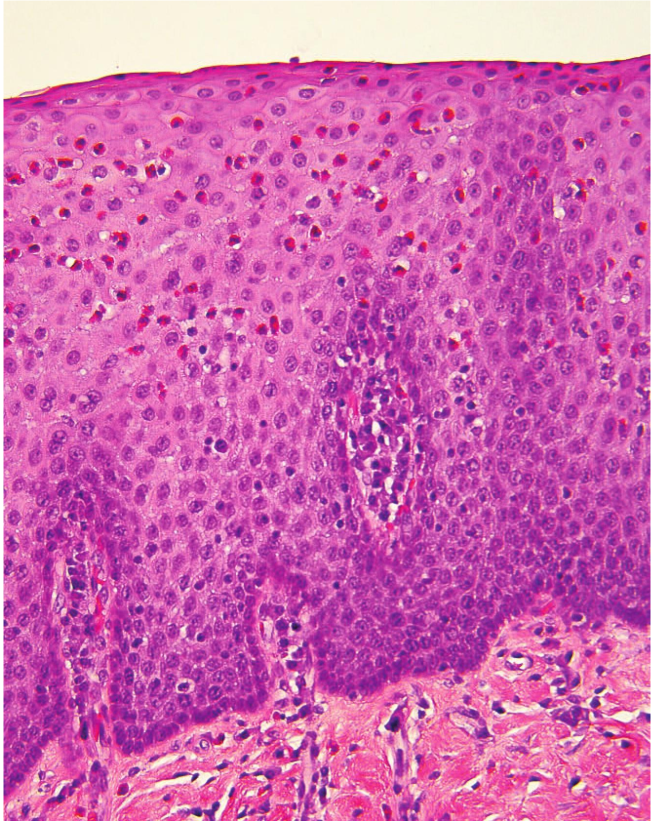


FIGURE VII-14B

Which of the following is the most appropriate first step in management?

A. Elimination diet
B. IV methylprednisolone
C. Mepolizumab
D. Trial of a proton pump inhibitor
E. Topical corticosteroids

VII-15. Ms. Pole is a 54-year-old woman who presents with recurrent episodes of chest discomfort at rest. She denies exertional dyspnea and reports that occasionally her pain is relieved with antacids. She works as a health care consultant and has frequent stressful battles with doctors and hospitals. An exercise cardiac stress test does not reveal any evidence of inducible ischemia. She has a barium swallow, which is shown in Figure VII-15. You suspect that she has diffuse esophageal spasm. Which of the following findings on esophageal manometry would support that diagnosis?

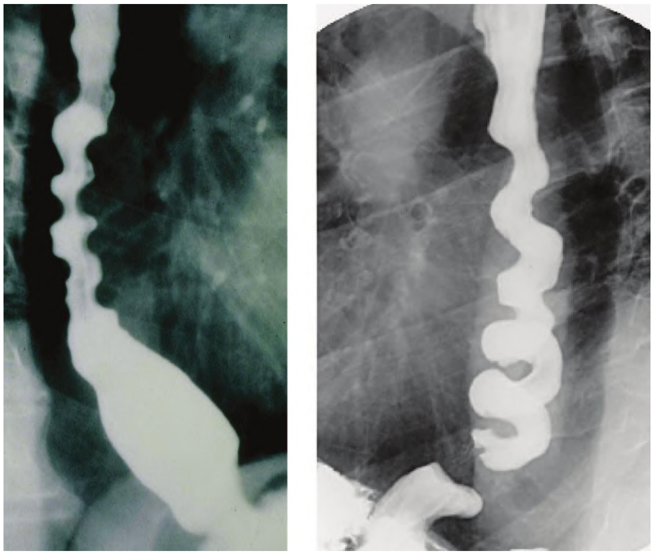


FIGURE VII-15

A. Contractions in the distal esophagus with short latency relative to the time of the pharyngeal contraction
B. Hypertensive peristalsis
C. Impaired lower esophageal sphincter (LES) contraction and absent peristalsis with substantial fluid pressurization of the esophageal body
D. Impaired LES contraction and absent peristalsis with no fluid pressurization of the esophageal body
E. Impaired LES contraction and absent peristalsis with spastic esophageal contractions

VII-16. Which of the following statements regarding therapy for gastroesophageal reflux (GERD) therapy is TRUE?

A. *Clostridium difficile* infection rates are decreased in patients receiving proton pump inhibitors.
B. Histamine-2 receptor antagonists are more effective than proton pump inhibitors.
C. The effectiveness of proton pump inhibitors increases substantially with increased dose.
D. Proton pump inhibitors are a rare cause of interstitial nephritis.
E. Weight loss has been proven in randomized controlled trials to ameliorate the symptoms of GERD.

VII-17. A 58-year-old man is evaluated for abdominal pain by his primary care physician. He reports severe stress at the job for the last 3 months and has since noted that he has epigastric pain that is relieved by eating and drinking milk. He has not had food regurgitation, dysphagia, or bloody emesis or bowel movements. He denies any symptoms in his chest. Peptic ulcer disease is suspected. Which of the following statements regarding noninvasive testing for *Helicobacter pylori* is true?

A. There is no reliable noninvasive method to detect *H. pylori*.
B. Stool antigen testing is appropriate for proof of cure after therapy for *H pylori*.
C. Plasma antibodies to *H. pylori* offer the greatest sensitivity for diagnosis of infection.
D. Exposure to low-dose radiation is a limitation to urea breath test.
E. False-negative test results using the urea breath test may occur with recent use of nonsteroidal anti-inflammatory drugs.

VII-18. A 44-year-old woman complains of 6 months of epigastric pain that is worst between meals. She also reports symptoms of heartburn. The pain is typically relieved by over-the-counter antacid medications. She comes to the clinic after noting her stools darkening. She has no significant past medical history and takes no medications. Her physical examination is normal except for diffuse mid-epigastric pain. Her stools are heme positive. She undergoes esophagogastroduodenoscopy, which demonstrates a well-circumscribed, 2-cm duodenal ulcer that is positive for *Helicobacter pylori*. Which of the following is the recommended initial therapy given these findings?

A. Lansoprazole, clarithromycin, and metronidazole for 14 days
B. Pantoprazole and amoxicillin for 21 days
C. Pantoprazole and clarithromycin for 14 days
D. Omeprazole, bismuth, tetracycline, and metronidazole for 14 days
E. Omeprazole, metronidazole, and clarithromycin for 7 days

VII-19. A 57-year-old man with peptic ulcer disease experiences transient improvement with *Helicobacter pylori* eradication. However, 3 months later, symptoms recur despite acid-suppressing therapy. He does not take nonsteroidal anti-inflammatory drugs. Stool analysis for *H. pylori* antigen is negative. Upper gastrointestinal (GI) endoscopy reveals prominent gastric folds together with the persistent ulceration in the duodenal bulb previously detected and the beginning of a new ulceration 4 cm proximal to the initial ulcer. Fasting gastrin levels are elevated, and basal acid secretion is 15 mEq/h. What is the best test to perform to make the diagnosis?

A. No additional testing is necessary.
B. Blood sampling for gastrin levels following a meal.
C. Blood sampling for gastrin levels following secretin administration.
D. Endoscopic ultrasonography of the pancreas.
E. Genetic testing for mutations in the *MEN1* gene.

VII-20. Which of the following are side effects of therapies directed at peptic ulcer disease?

A. Famotidine may have weak anti-androgenic side effects resulting in reversible gynecomastia and impotence, primarily in patients receiving high doses for prolonged periods of time (months to years).
B. Long-term acid suppression, particularly with proton pump inhibitors, has been associated with a higher incidence of community-acquired pneumonia as well as community- and hospital-acquired *Clostridium difficile*–associated disease.
C. Magnesium hydroxide can produce constipation and phosphate depletion.
D. Rebound gastric acid hypersecretion has been described in *H. pylori*–negative individuals after discontinuation of H_2 blockers. It occurs even after relatively short-term usage (2 months) and may last for up to 2 months after the medication has been discontinued.
E. The long-term use of aluminum hydroxide can lead to milk-alkali syndrome (hypercalcemia, hyperphosphatemia with possible renal calcinosis and progression to renal insufficiency).

VII-21. Which of the following statements regarding gastric acid secretion is true?

A. Basal acid production occurs in a circadian pattern, with highest levels occurring during the morning and lowest levels during the night.
B. Distention of the stomach wall directly activates acid secretion by parietal cells.
C. Sight, smell, and taste of food are the components of the cephalic phase, which stimulates gastric secretion via the phrenic nerve.
D. The gastric phase is activated once food enters the stomach. This component of secretion is driven by nutrients (amino acids and amines) that directly (via peptone and amino acid receptors) and indirectly (via stimulation of intramural gastrin releasing peptide neurons) stimulate the G cell to release gastrin, which in turn activates the parietal cell via direct and indirect mechanisms.

VII-22. A 23-year-old woman is evaluated by her primary care physician for diffuse, crampy abdominal pain. She reports that she has had abdominal pain for the last several years, but it is getting worse and is now associated with intermittent diarrhea without flatulence. This does not wake her at night. Stools do not float and are not hard to flush. She has not noted any worsening with specific foods, but she does have occasional rashes on her lower legs. She has lost about 10 lb over the last year. She is otherwise healthy and takes no medications. Which of the following is the most appropriate recommendation at this point?

A. Increased dietary fiber intake
B. Measurement of antiendomysial antibody
C. Measurement of 24-hour fecal fat
D. Referral to gastroenterologist for endoscopy
E. Trial of lactose-free diet

VII-23. A 54-year-old man is evaluated by a gastroenterologist for diarrhea that has been present for approximately 1 month. He reports stools that float and are difficult to flush down the toilet; these can occur at any time of day or night but seem worsened by fatty meals. In addition, he reports pain in many joints lasting days to weeks and not relieved by ibuprofen. His wife notes that the patient has had difficulty with memory for the last few months. He has lost 30 lb and reports intermittent low-grade fevers. He takes no medications and is otherwise healthy. Endoscopy is recommended. Which of the following is the most likely finding on small bowel biopsy?

A. Dilated lymphatics
B. Flat villi with crypt hyperplasia
C. Mononuclear cell infiltrate in the lamina propria
D. Normal small bowel biopsy
E. Periodic acid–Schiff-positive macrophages containing small bacilli

VII-24. A 54-year-old man presents with 1 month of diarrhea. He states that he has 8 to 10 loose bowel movements a day. He has lost 8 lb during this time. Vital signs and physical examination are normal. Serum laboratory studies are normal. A 24-hour stool collection reveals 500 g of stool with a measured stool osmolality of 200 mOsm/L and a calculated stool osmolality of 210 mOsm/L. Based on these findings, which of the following is the most likely cause of this patient's diarrhea?

A. Celiac sprue
B. Chronic pancreatitis
C. Lactase deficiency
D. Vasoactive intestinal peptide tumor
E. Whipple disease

VII-25. All of the following are direct functions of the intestinal epithelium **EXCEPT**:

A. Barrier and immune defense
B. Fluid and electrolyte absorption and secretion
C. Production of several bioactive amines and peptides
D. Secretion of bile acids
E. Synthesis and secretion of apolipoproteins

VII-26. A 40-year-old male with multiple prior admissions for alcoholic pancreatitis presents for evaluation of several months of diarrhea. A 24-hour stool analysis confirms that he has steatorrhea. Which of the following mechanisms likely explains the elevation in stool fat content and resulting diarrhea?

A. Abnormalities of intestinal lymphatics (e.g., intestinal lymphangiectasia)
B. Decreased enterohepatic circulation of bile acids
C. Decreased hydrolysis of triglycerides to free fatty acids, monoglycerides, and glycerol
D. Impaired lipid absorption as a result of mucosal inflammation
E. Increased dietary intake of medium chain triglycerides

VII-27. A 24-year-old woman is admitted to the hospital with a 1-year history of severe abdominal pain and chronic diarrhea that has been bloody for the past 2 months. She reports a 20-lb weight loss, frequent fevers, and night sweats. She denies vomiting. Her abdominal pain is crampy and primarily involves her right lower quadrant. She is otherwise healthy. Examination is concerning for an acute abdomen with rebound and guarding present. CT shows free air in the peritoneum. She is urgently taken to the operating room for surgical exploration, where she is found to have multiple strictures and a perforation of her bowel in the terminal ileum. The rectum was spared, and a fissure from the duodenum to the jejunum was found. The perforated area is resected and adhesions lysed. Which of the following findings on pathology of her resected area confirms her diagnosis?

A. Crypt abscesses
B. Flat villi
C. Noncaseating granulomas throughout the bowel wall
D. Special stain for *Clostridium difficile* toxin
E. Transmural acute and chronic inflammation

VII-28. A 45-year-old man with ulcerative colitis has been treated for the last 5 years with infliximab with excellent resolution of his bowel symptoms and endoscopic evidence of normal colonic mucosa. He is otherwise healthy. He is evaluated by a dermatologist for a lesion that initially was a pustule over his right lower extremity but has since progressed in size with ulceration. The ulcer is moderately painful. He does not recall any trauma to the area. On examination, the ulcer measures 15 × 7 cm, and central necrosis is present. The edges of the ulcer are violaceous. No other lesions are identified. Which of the following is the most likely diagnosis?

A. Erythema nodosum
B. Metastatic Crohn disease
C. Psoriasis
D. Pyoderma gangrenosum
E. Pyoderma vegetans

VII-29. Which of the following statements regarding the epidemiology of inflammatory bowel disease (IBD) is true?

A. Children who receive frequent antibiotics in childhood are at lower risk of developing IBD.
B. IBD appears with decreasing incidence in countries that are becoming more westernized.
C. Patients who have had an appendectomy with confirmed appendicitis have a lower risk of developing ulcerative colitis.
D. Peak incidence of ulcerative colitis and Crohn disease is in the 6th–7th decades of life.
E. The highest incidence rates of ulcerative colitis and Crohn disease have been reported in Asia, the Middle East, and Northern Africa.

VII-30. A 36-year-old male has had Crohn disease for 5 years. His disease was initially managed with occasional tapers of oral prednisone, followed by use of oral budesonide. Over the last 6 months he has required two courses of oral prednisone and was hospitalized for worsening abdominal pain and fevers requiring IV antibiotics and corticosteroids. He has not had evidence of fistulizing disease. How should his Crohn disease be managed at this time?

A. Begin IV cyclosporine A
B. Provide intermittent infusions of infliximab each time he has a disease flare
C. Start azathioprine orally at 2–3mg/kg with the potential addition of infliximab
D. Start maintenance prednisone at 0.5mg/kg for 3 months
E. Start monthly infusions of IV golimumab

VII-31. Which of the following patients requires no further testing before making the diagnosis of irritable bowel syndrome and initiating treatment?

A. A 76-year-old woman with 6 months of intermittent crampy abdominal pain that is worse with stress and associated with bloating and diarrhea.
B. A 25-year-old woman with 6 months of abdominal pain, bloating, and diarrhea that has worsened steadily and who now wakes from sleep at night to move her bowels.
C. A 30-year-old man with 6 months of lower abdominal crampy pain relieved with bowel movements, usually loose. Symptoms are worse during the daytime at work and better on the weekend. Weight loss is not present.
D. A 19-year-old female college student with 2 months of diarrhea and worsening abdominal pain with occasional blood in her stool.
E. A 27-year-old woman with 6 months of intermittent abdominal pain, bloating, and diarrhea without associated weight loss. Crampy pain and diarrhea persist after a 48-hour fast.

VII-32. A 29-year-old woman comes to see you in the clinic because of abdominal discomfort. She feels abdominal discomfort on most days of the week, and the pain varies in location and intensity. She notes constipation as well as diarrhea, but diarrhea predominates. Compared with 6 months ago, she has more bloating and flatulence than she has had before. She identifies eating and stress as aggravating factors, and her pain is relieved by defecation. You suspect irritable bowel syndrome. Laboratory data include white blood cell count 8000/μL, hematocrit 32%, platelets 210,000/μL, and erythrocyte sedimentation rate 44 mm/h. Stool studies show the presence of lactoferrin but no blood. Which of the following interventions is most appropriate at this time?

A. Antidepressants
B. Ciprofloxacin
C. Colonoscopy
D. Reassurance and patient counseling
E. Stool bulking agents

VII-33. Which of the following statements regarding the pathophysiology of irritable bowel syndrome (IBS) is true?

A. Abdominal distention, belching, and flatulence are most commonly due to increased amounts of gas in the gastrointestinal tract of patients with IBS.
B. Compared with patients without IBS, IBS patients frequently exhibit blunted sensory responses to visceral stimulation.
C. Gut dysbiosis acting in concert with genetic and environmental factors may alter intestinal permeability, increase antigen presentation resulting in mast cell activation.
D. Almost all patients with IBS display persistent signs of low-grade mucosal inflammation with activated lymphocytes, mast cells, and enhanced expression of proinflammatory cytokines.
E. The majority of IBS patients report a bout of gastroenteritis at the onset of their symptoms.

VII-34. A 34-year-old female with known irritable bowel syndrome has severe bouts of postprandial pain that have prevented her from being able to enjoy regular meals with her family. Which of the following therapies would be most likely to improve her discomfort?

A. Activated charcoal taken immediately after eating a meal.
B. An anticholinergic drug, such as dicyclomine, administered 30 minutes prior to eating.
C. Citalopram administered once daily.
D. Fiber supplementation with psyllium.
E. Small doses of loperamide prior to meals.

VII-35. A 78-year-old woman is admitted to the hospital with fever, loss of appetite, and left lower quadrant pain. She is not constipated but has not moved her bowels recently. Laboratory examination is notable for an elevated white blood cell count. These symptoms began approximately 3 days ago and have steadily worsened. Which of the following statements regarding her likely condition is true?

A. Air-fluid levels are commonly seen on plain abdominal films.
B. Less than 25% of patients present with peritoneal signs.
C. Lower gastrointestinal bleeding will likely be visualized on CT angiography.
D. Thickened colonic wall is not required on CT for the diagnosis of her likely condition.
E. Ultrasound of the pelvis is the best modality to visualize the likely pathologic process.

VII-36. A 67-year-old man is evaluated by the emergency department for blood in the toilet bowl after moving his bowels. Blood was also present on the toilet paper after wiping. He does report straining and recent constipation. He has a history of systemic hypertension and hyperlipidemia. Vital signs are normal, and he is not orthostatic. Anoscopy shows external hemorrhoids, hematocrit is normal, and bleeding does not recur during his 6-hour emergency department stay. Which of the following is the most appropriate management?

A. Ciprofloxacin and metronidazole
B. Cortisone suppositories and fiber supplementation
C. Hemorrhoidal banding
D. Operative hemorrhoidectomy
E. Upper endoscopy

VII-37. An 88-year-old woman is brought to your clinic by her family because she has become increasingly socially withdrawn. The patient lives alone and has been reluctant to visit or be visited by her family. Family members, including seven children, also note a foul odor in her apartment and on her person. She has not had any weight loss. Alone in the examining room, she only complains of hemorrhoids. On mental status examination, she does have signs of depression. Which of the following interventions is most appropriate at this time?

A. Head CT scan
B. Treatment with an antidepressant medication
C. Physical examination including genitourinary and rectal examination
D. Screening for occult malignancy
E. Serum thyroid-stimulating hormone

VII-38. A 59-year-old female develops acute diverticulitis and requires hospitalization for IV antibiotics. She has a CT scan that does not show evidence of abscess perforation, stricture, or fistula, and she improves in about a week. Which of the following should be undertaken to prevent further symptomatic disease?

A. Annual colonoscopy
B. Avoidance of nuts
C. Daily mesalamine therapy
D. Initiation of a high-fiber diet
E. Subtotal colectomy to reduce the risk of perforation during a subsequent bout

VII-39. A 63-year-old man with poorly controlled type 2 diabetes presents to his primary care physician with 3 days or perianal pain, fever, and difficulty voiding. He has a history of uncomplicated stage 1 hemorrhoids, which have been treated in the past with cortisone suppositories and a high-fiber diet. On examination, he is febrile and there is a 2-cm fluctuant mass at the anal verge. Which of the following would be the most appropriate management?

A. Excision and drainage of the mass
B. Infrared anticoagulation
C. Oral antibiotics and follow-up in 2 days
D. Rubber band ligation
E. Sclerotherapy

VII-40. A 63-year-old man with a history of diabetes and myocardial infarction was admitted to the medical intensive care unit 1 day ago with sepsis due to pneumococcal pneumonia with bacteremia. He was started on antibiotics immediately, but he initially required high doses of noradrenaline and fluids to stabilize his blood pressure. The noradrenaline was weaned off approximately 12 hours ago. Over the past 2 hours, he has had increasing abdominal pain, distension, and bloody stools. His physical examination is notable for blood pressure of 100/50, regular heart rate of 100 beats/min, respiratory rate of 22 breaths/min, and oxygen saturation of 93% on high-flow nasal oxygen. He has a diffusely tender abdomen with no audible bowel sounds. An abdominal radiograph shows multiple small bowel air-fluid levels. Which of the following is the most likely diagnosis?

A. Arterial embolism
B. *Clostridium difficile* colitis
C. Inflammatory bowel disease
D. Nonocclusive mesenteric ischemia
E. Venous thrombosis

VII-41. A 79-year-old female with known coronary artery disease requiring previous percutaneous coronary intervention with stent placement presents to her primary care physician's office with 3 months of cramping abdominal pain after meals. She denies any change in the pain with defecation, and does not report increased flatulence or belching. She has had more frequent, loose stools but denies constipation. She has lost 15 lb during this time period. Which of the following would be the most appropriate next step in management?

A. Noncontrast CT scan of the abdomen and pelvis
B. Electrocardiogram to look for the presence of atrial fibrillation
C. Initiation of a high fiber diet
D. Initiation of an selective serotonin reuptake inhibitor medication for possible depression
E. Mesenteric angiography

VII-42. A 74-year-old woman is 2 days post hip surgery for a fracture after a fall. Her only medication prior to admission was a calcium supplement, and she has no prior surgical history. Over the past 24 hours, she has had increasing abdominal discomfort and distension. She received a dose of cefazolin prior to surgery but no other antibiotics. On physical examination, she is afebrile with a blood pressure of 140/80, heart rate of 110 beats/min, respiratory rate of 16 breaths/min, and oxygen saturation of 100% on 2 L of nasal oxygen. She has a distended tympanic abdomen with absent bowel sounds. There is no rebound tenderness. Her upright abdominal film is shown in Figure VII-42. Which of the following is the most likely diagnosis?

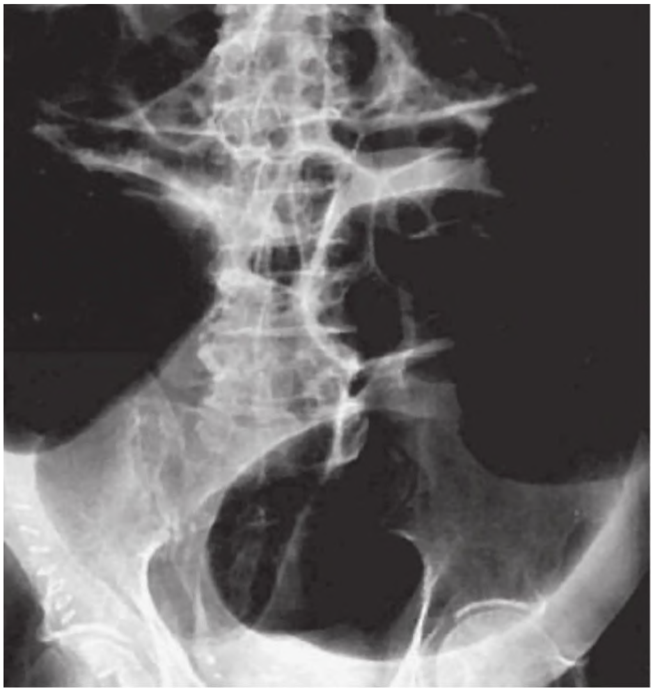


FIGURE VII-42 Reproduced with permission from Bongard FS et al: *Current Critical Care Diagnosis & Treatment.* New York: McGraw Hill, 1994.

A. Acalculous cholecystitis
B. Colonic pseudo-obstruction
C. Perforated duodenal ulcer
D. Small bowel obstruction
E. Small bowel ileus

VII-43. A 52-year-old man presents to the emergency department with acute-onset abdominal pain that awoke him from sleep. He has a history of paroxysmal atrial fibrillation but has not had any recent episodes of atrial fibrillation on remote monitoring. He has no prior history of abdominal surgeries. His pain is 7/10 in severity, and comes in intense waves. He has vomited twice and each time his pain was improved for a few minutes afterward, but then it returned. He is afebrile, with a heart rate in the 120s that is confirmed to be sinus tachycardia by electrocardiogram. He is afebrile. His abdomen is tender and distended. He has high-pitched "musical" bowel sounds. CT of the abdomen is shown in Figure III-43. He has no evidence of gallstones or ductal dilatation on right upper quadrant ultrasound, and the pancreas appears normal on

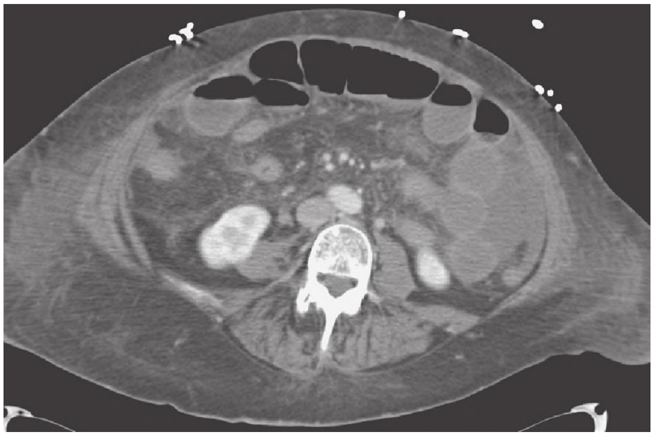


FIGURE VII-43

CT (not shown). Labs are pending. Which of the following is the most likely cause of his symptoms?

A. Acute mesenteric ischemia
B. Acute cholecystitis
C. Acute pancreatitis
D. Small bowel obstruction
E. Viral gastroenteritis

VII-44. A 32-year-old woman is evaluated in the emergency department for abdominal pain. She reports a vague loss of appetite for the last day and has had progressively severe abdominal pain, initially at her umbilicus, but now localized to her right lower quadrant. The pain is crampy. She has not moved her bowels or vomited. She reports that she is otherwise healthy and has had no sick contact. Examination is notable for a temperature of 38.2°C (100.7°F) and heart rate of 105 beats/min; otherwise, vital signs are normal. Her abdomen is tender in the right lower quadrant, and pelvic examination is normal. Urine pregnancy test is negative. Which of the following imaging modalities is most likely to confirm her diagnosis?

A. CT of the abdomen without contrast
B. Colonoscopy
C. Pelvic ultrasound
D. Plain film of the abdomen
E. Ultrasound of the abdomen

VII-45. The patient in question VII-44 is diagnosed with acute appendicitis. Which of the following is the most important next step in management?

A. Colonoscopy
B. Empiric antibiotics and watchful waiting for 48 hours
C. Exploratory laparotomy
D. IV corticosteroids
E. Laparoscopic appendectomy

VII-46. A 38-year-old man is seen in the urgent care center with several hours of severe abdominal pain. His symptoms began suddenly, but he reports several months of pain in the epigastrium after eating, with a resultant 10-lb weight loss. He takes no medications other than over-the-counter antacids and has no other medical problems or habits. On physical examination, temperature is 38.0°C (100.4°F), pulse is 130 beats/min, respiratory rate is 24 breaths/min, and blood pressure is 110/50. His abdomen has absent bowel sounds and is rigid with involuntary guarding diffusely. A plain film of the abdomen is obtained and shows free air under the diaphragm. Which of the following is most likely to be found in the operating room?

A. Necrotic bowel
B. Necrotic pancreas
C. Perforated duodenal ulcer
D. Perforated gallbladder
E. Perforated gastric ulcer

VII-47. Which of the following statements regarding the signs and symptoms of a patient with acute appendicitis is true?

A. Anorexia is an uncommon symptom.
B. McBurney point describes pain in the mid-epigastrium.
C. Patients with pelvic appendicitis commonly present with dysuria, urinary frequency, diarrhea, or tenesmus.
D. Right lower quadrant tenderness is present in only 50% of patients.
E. Rovsing sign is the most sensitive finding on physical examination.

VII-48. The greatest source of nutrients and calories in a typical individual's diet come from which source?

A. Alcohol
B. Carbohydrates
C. Fat
D. Protein

VII-49. Which of the following factors accounts for the largest amount of water loss per day?

A. Evaporation and exhalation
B. Fever
C. Normal stool output (i.e., no diarrhea)
D. Pregnancy
E. Urine output in a person with a very low solute diet

VII-50. Mr. Ryan is a 56-year-old man who was admitted to the surgical service for care due to exposure injury and frostbite in his distal extremities. He has a long-standing history of alcoholism, drinking about 1 L of vodka on a daily basis. You are asked to consult due to concerns of bizarre behaviors exhibited by the patient. He is expressing a belief that his wounds were the result of burns that were inflicted on him by "torturers" in the government because he "knows too much" about government surveillance plans. The surgical team reports it is difficult to keep the patient in his bed, and he seems unsteady on his feet at times. He has been medicated throughout his stay for prevention of alcohol withdrawal via a symptom-triggered approach and last received lorazepam 2 mg orally about 2 hours ago. At that time, the patient was noted to be tremulous, tachycardic, and hypertensive. The delusional thoughts are not responsive to treatment of alcohol withdrawal symptoms. When you see the patient, he is sleeping quietly. Vital signs are blood pressure 110/82, heart rate 94 beats/min, respiratory rate 16 breaths/min, temperature 37.1°C (98.7°F), and SaO_2 is 97% on room air. He awakens easily and has a minimal resting tremor. On neurologic examination, he exhibits past-pointing, difficulty with rapid alternating movements, horizontal nystagmus, and decreased sensation to light touch and pinprick in the lower extremities below the mid-tibia. His gait is wide based and ataxic. He no longer expresses his prior delusional beliefs, but he is disoriented and thinks he is in jail. He states he was brought to "this gulag" so that the government could experiment on him. He has 5% dextrose in half-normal saline infusing at 100 mL/h and is also receiving nafcillin 2 g IV every 4 hours for cellulitis. Which of the following is the most likely cause of Mr. Ryan's altered mental state and neurologic findings?

A. Hypoglycemia
B. Hyponatremia
C. Niacin deficiency
D. Thiamine deficiency
E. Undertreated alcohol withdrawal

VII-51. A 48-year-old man is diagnosed with carcinoid syndrome after presenting with diarrhea, flushing, and hypotension. With appropriate treatment, he experiences an appropriate response biochemically, and his flushing and blood pressure are markedly improved. However, he continues to have some mild diarrhea and also has mouth soreness. He remains fatigued with a loss of appetite and irritability. On examination, you notice his tongue is bright red and somewhat enlarged. It is tender to touch. In addition, he has a pigmented and scaling rash that is most prominent around his neckline. Which of the following is the most likely vitamin or mineral deficiency in this patient?

A. Copper
B. Niacin
C. Riboflavin
D. Vitamin C
E. Zinc

VII-52. A 51-year-old alcoholic man presents to the emergency department complaining of vomiting blood. On further evaluation including gastric lavage, you determine that he is not experiencing an upper gastrointestinal bleed, but he is having significant gingival bleeding. He is intoxicated and complains of fatigue. Reviewing his chart, you find that he had a hemarthrosis evacuated 6 months ago and has been lost to follow-up since then. He takes no medications. Laboratory data show platelets of 250,000 and international normalized ratio of 0.9. He has a diffuse hemorrhagic eruption on his legs that is centered around hair follicles. Which of the following is the recommended treatment for this patient's underlying disorder?

A. Folate
B. Niacin
C. Thiamine
D. Vitamin C
E. Vitamin K

VII-53. A 46-year-old male from Mexico was found to be purified protein derivative–positive on routine health screening prior to beginning a new job in a hospital. He was started on isoniazid for treatment of latent tuberculosis. Three months into his treatment course he develops numbness and tingling in his bilateral feet. On laboratory assessment his liver function tests are normal. He reports taking his isoniazid faithfully but does not remember being told to take any additional medications along with the isoniazid. Which of the following is the likely cause of his symptoms?

A. Niacin deficiency
B. Thiamine deficiency
C. Vitamin A toxicity
D. Vitamin B_6 deficiency
E. Vitamin B_{12} deficiency

VII-54. A 3-year-old who recently arrived from Indonesia comes in for a routine wellness check with his new adoptive parents. On physical examination he is noted to have white patches of keratinized epithelium appearing on the sclera. Which of the following would be the most appropriate treatment for this condition?

A. Biotin 10 mg/day for 7 days
B. Pyridoxine 50 mg/day for 14 days
C. Vitamin A 200,000 IU orally on day 1, day 2, and day 15
D. Vitamin B_{12} 1000 mcg per day for 1 month
E. Vitamin C 100 mg/day for 7 days

VII-55. A 21-year-old woman is admitted to the cardiac care unit after collapsing in her college dormitory. When emergency personnel arrived, she was found to be in a torsades de pointes arrhythmia and was pulseless. She received cardiopulmonary resuscitation, defibrillation, and magnesium en route to the hospital. On arrival, her initial potassium is 1.2 mEq/L. Her physical examination is remarkable for an excessively thin appearance with lanugo hair on arms and chest. Her body mass index is 14.6 kg/m^2.

Which of the following statements is true regarding this patient's nutritional state?

A. Mortality in the disease is most commonly due to complications of malnutrition.
B. Poor wound healing and frequent skin infections are common complications.
C. Systemic inflammation is a predominant finding on laboratory examination.
D. The serum albumin is typically less than 2.8 g/dL.
E. Triceps skinfold <3 mm and mid-arm muscle circumference <15 cm are useful diagnostic criteria.

VII-56. You are caring for a 54-year-old woman in the intensive care unit who was admitted for treatment of severe sepsis and pneumonia. You would like to initiate enteral nutrition and plan to calculate basal energy expenditure for the patient. All of the following factors are used to determine the patient's caloric needs EXCEPT:

A. Age
B. Albumin
C. Gender
D. Height
E. Weight

VII-57. Which of the following conditions would be best classified as starvation-associated malnutrition?

A. Closed head injury
B. Major depression
C. Motor-vehicle accident
D. Pancreatic cancer
E. Sarcopenic obesity

VII-58. Which of the following statements regarding the methodologies for determining body composition and nutritional status is true?

A. Albumin is useful in assessing nutritional status because of its long half-life.
B. Anthropomorphic analyses such as measuring skinfolds and circumferences are reliable and reproducible.
C. Bioelectrical impedance can be readily applied and interpreted in individuals of different races and ethnic groups.
D. C-reactive protein is a specific marker for malnutrition.
E. Dual energy x-ray absorptiometry scanning can be used to compare truncal and appendicular soft tissue.

VII-59. Which of the following is the most common symptom or sign of liver disease?

A. Fatigue
B. Itching
C. Jaundice
D. Nausea
E. Right upper quadrant pain

VII-60. All of the following are CAGE questions, which should be a component of the medical history focusing on alcohol abuse and dependence, EXCEPT:

A. Do you feel like you have a greater tolerance for alcohol than your friends?
B. Have you ever felt you ought to cut down on your drinking?
C. Have people annoyed you by criticizing your drinking?
D. Have you ever felt guilty or bad about your drinking?
E. Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover?

VII-61. A 43-year-old female presents to her primary care physician with fatigue and malaise. On routine laboratory testing she is found to have an aspartate aminotransferase of 150 IU/L, and alanine aminotransferase of 165 IU/L, an alkaline phosphatase of 125 IU/L, a total bilirubin of 1.2 mg/dL, and an international normalized ratio of 0.9. Which of the following best describes the pattern of liver tests?

A. Cholestatic
B. Cirrhotic
C. Hepatocellular
D. Mixed
E. Peritonitic

VII-62. All of the following are potential advantages of magnetic resonance cholangiopancreatography over endoscopic retrograde cholangiopancreatography EXCEPT:

A. Faster image acquisition
B. Higher sensitivity for identifying ampullary lesions
C. No risk of ionizing radiation
D. No risk of pancreatitis
E. No need for contrast media

VII-63. Elevation in all of the following laboratory studies would be indicative of liver disease EXCEPT:

A. 5′-Nucleotidase
B. Aspartate aminotransferase
C. Conjugated bilirubin
D. Unconjugated bilirubin
E. Urine bilirubin

VII-64. Which of the following statements regarding liver function tests is true?

A. Alanine aminotransferase (ALT) is found in liver, cardiac muscle, skeletal muscle, and kidney.
B. Elevation of aspartate aminotransferase (AST) and ALT to >1000 IU/L is typical of ischemic hepatitis.
C. Elevation of AST is more specific for liver dysfunction than elevation of ALT.
D. Increased AST and ALT with an AST:ALT ratio of >3 is typical of acute viral hepatitis.
E. The magnitude of elevated AST and ALT has important prognostic significance in acute hepatitis.

VII-65. Which of the following is true about aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in liver injury?

A. A ratio of ALT:AST greater than 1 is suggestive of cirrhosis.
B. ALT is usually equal to or greater than AST in most causes of acute liver injury.
C. AST is often normal is cases of alcoholic cirrhosis.
D. AST and ALT usually remain elevated for days after the passage of a gallstone.
E. If the ALT:AST ratio is greater than 3, then alcoholic hepatitis should be suspected.

VII-66. Which of the following is true about biochemical liver testing?

A. γ-Glutamyl transpeptidase elevation is specific for cholestatic liver injury.
B. Increased IgM levels may be a marker of autoimmune hepatitis.
C. Low factor VIII levels may indicate chronic liver disease.
D. Patients over the age of 60 can have a mild elevation in their alkaline phosphatase levels up 1.5 times the upper limit of normal.
E. Serum albumin is a good marker of the severity of acute liver injury.

VII-67. A 26-year-old male resident is noticed by his attending physician to have yellow eyes after his 24-hour call period. When asked, the resident states he has no medical history and is a social drinker, but on occasion, he has thought he might have mild scleral icterus when he is stressed or has more than four to five alcoholic drinks. He never sought medical treatment because his eyes would return fully to normal within 2 days. He denies nausea, abdominal pain, dark urine, light-colored stools, pruritus, or weight loss. On examination, he has a body mass index of 20.1 kg/m^2, and his vital signs are normal. Scleral icterus is present. There are no stigmata of chronic liver disease. The patient's abdomen is soft and nontender. The liver span is 8 cm to percussion. The liver edge is smooth and palpable only with deep inspiration. The spleen is not palpable. Laboratory examinations are normal except for a total bilirubin of 3.0 mg/ dL. Direct bilirubin is 0.2 mg/dL. Aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase are normal. Hematocrit, lactate dehydrogenase, and haptoglobin are normal. Which of the following is the most likely diagnosis?

A. Autoimmune hemolytic anemia
B. Crigler-Najjar syndrome type 1
C. Choledocholithiasis
D. Dubin-Johnson syndrome
E. Gilbert syndrome

VII-68. Which of the following statements regarding the hyperbilirubinemia seen in patients with significant intravascular hemolysis is true?

A. Bilirubin values <4 mg/dL imply concomitant gallbladder or biliary dysfunction.
B. Bilirubin values >4 mg/dL (68 μmol/L) imply concomitant liver dysfunction.
C. It is typically composed of 50% conjugated and 50% unconjugated bilirubin.
D. Prolonged hemolysis may result in the development of cirrhosis.

VII-69. A 26-year-old female who is 3-months pregnant presents for a routine prenatal visit and is found to be jaundiced. This is her first pregnancy and she reports no symptoms other than occasional early morning nausea that resolves after eating breakfast. She has no pruritus. Her physical examination is unremarkable with the exception of obvious jaundice. She has no hepatosplenomegaly and her fundus is not yet palpable. Labs are notable for a total bilirubin of 6 mg/dL, with a direct bilirubin of 5 mg/dL. Her aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase levels are all within the normal range. Which of the following is the most likely cause of her hyperbilirubinemia?

A. Benign recurrent intrahepatic cholestasis
B. Cholestasis of pregnancy
C. Crigler-Najjar syndrome type 2
D. Dubin-Johnson syndrome
E. HELLP (hemolysis, elevated liver enzymes, and low platelet) syndrome

VII-70. A 34-year-old man presents to the physician complaining of yellow eyes. For the past week, he has felt ill, with decreased oral intake, low-grade fevers (~100°F), fatigue, nausea, and occasional vomiting. With the onset of jaundice, he has noticed pain in his right upper quadrant. He currently uses marijuana and ecstasy and has a prior history of injection drug use with cocaine. He has no other past medical history, but he was unable to donate blood for reasons that he cannot recall 4 years previously. His social history is remarkable for working as a veterinary assistant. On sexual history, he reports five male sexual partners over the past 6 months. He does not consistently use condoms. On physical examination, he appears ill and has obvious jaundice with scleral icterus. His liver is 15 cm to percussion, palpable 6 cm below the right costal margin. The edge is smooth and tender to palpation. The spleen is not enlarged. There are no stigmata of chronic liver disease. His aspartate aminotransferase is 1232 IU/L, alanine aminotransferase is 1560 IU/L, alkaline phosphatase is 394 IU/L, total bilirubin is 13.4 mg/dL, and direct bilirubin is 12.2 mg/dL. His international normalized ratio is 2.3, and activated partial thromboplastin time is 52 seconds. Hepatitis serologies are sent and reveal the following:

Hepatitis A IgM: negative
Hepatitis A IgG: negative
Hepatitis B core IgM: positive
Hepatitis B core IgG: negative
Hepatitis B surface antigen: positive

Hepatitis B surface antibody: negative
Hepatitis B e antigen: positive
Hepatitis B e antibody: negative
Hepatitis C antibody: positive

What is the cause of the patient's current clinical presentation?

A. Acute hepatitis A infection
B. Acute hepatitis B infection
C. Acute hepatitis C infection
D. Chronic hepatitis B infection
E. Drug-induced hepatitis

VII-71. In the patient described in question VII-70, what would be the best approach to prevent development of chronic hepatitis?

A. Administration of anti-hepatitis A virus IgG
B. Administration of lamivudine
C. Administration of pegylated interferon-α plus ribavirin
D. Administration of prednisone beginning at a dose of 1 mg/kg daily
E. Do nothing and observe as 99% of individuals with this disease recover

VII-72. A 16-year-old girl had visited your clinic 1 month ago with jaundice, vomiting, malaise, and anorexia. Two other family members were ill with similar symptoms. Based on viral serologies, including a positive anti-hepatitis A virus IgM, a diagnosis of hepatitis A was made. The patient was treated conservatively, and 1 week after first presenting, she appeared to have made a full recovery. She returns to your clinic today complaining of the same symptoms she had 1 month ago. She is jaundiced, and an initial panel of laboratory tests returns elevated transaminases. Which of the following offers the best explanation of what has occurred in this patient?

A. Co-infection with hepatitis C
B. Inappropriate treatment of initial infection
C. Incorrect initial diagnosis; this patient likely has hepatitis B
D. Reinfection with hepatitis A
E. Relapse of hepatitis A

VII-73. An 18-year-old man presents to a rural clinic with nausea, vomiting, anorexia, abdominal discomfort, myalgias, and jaundice. He describes occasional alcohol use and is sexually active. He describes using heroin and cocaine "a few times in the past." He works as a short-order cook in a local restaurant. He has lost 15.5 kg (34 lb) since his last visit to the clinic and appears emaciated and ill. On examination, he is noted to have icteric sclerae and a palpable, tender liver below the right costal margin. In regard to acute hepatitis, which of the following is true?

A. A distinction between viral etiologies cannot be made using clinical criteria alone.
B. Based on age and risk factors, he is likely to have a hepatitis B infection.
C. He does not have hepatitis E virus, as this infects only pregnant women.
D. This patient cannot have hepatitis C because his presentation is too acute.
E. This patient does not have hepatitis A because his presentation is too fulminant.

VII-74. Which of the following best explains why neonatal infection with hepatitis B virus (HBV) does not result in significant hepatocellular inflammation early in life?

A. Effective priming of HBV-specific T cells with HBV leads to the lack of an immune response.
B. HBV does not easily cross the placenta.
C. In utero exposure to HBV induces immune tolerance.
D. Maternal antibodies against hepatitis core antigen result in immunity against infection.
E. Natural killer cells are not particularly effective early in life.

VII-75. A 57-year-old female presents to your clinic for a routine health evaluation. She is complaining of intermittent abdominal pain so you decide to order serum chemistries. Her aspartate aminotransferase is mildly elevated at 75 IU/L, and her alanine aminotransferase is also mildly elevated at 66 IU/L. Her bilirubin and international normalized ratio are normal. She denies recent alcohol use and has never used injection drugs. She is sexually active and has had two recent male partners. She does not use barrier protection. She was born in China but has lived in the United States for 40 years. You decide to check hepatitis serologies and obtain the following results:

Hepatitis B surface antigen: positive
Hepatitis B surface antibody: negative
Hepatitis B core antibody: positive
Hepatitis B e-antigen: negative
Hepatitis B e-antibody: positive

Which of the following best describes her hepatitis B status?

A. Acute hepatitis B
B. Chronic Hepatitis B, high infectivity
C. Immunization against hepatitis B
D. Late acute or chronic hepatitis B, low infectivity
E. Recovery from hepatitis B

VII-76. Which of the following statements is true about the prevention of viral hepatitis?

A. Health care workers in endemic areas should receive the hepatitis D vaccine every 5 years.
B. Patients with acute hepatitis A should be placed on contact isolation to prevent transmission to health care workers and other patients.
C. Serum Ig has been shown to be effective in postexposure prophylaxis for hepatitis C.
D. The hepatitis B vaccine is a live attenuated vaccine that should be avoided in immunocompromised patients.
E. There is an effective vaccine against hepatitis E genotype 1 that also has effectiveness against other genotypes.

VII-77. A 32-year-old woman is admitted to the intensive care unit following an overdose of acetaminophen with co-ingestion of alcohol. She was known to be alert and interactive about 4 hours prior to her presentation when she had a fight with her boyfriend who then left the home. When he returned 6 hours later, he found an empty bottle of acetaminophen 500-mg capsules as well as an empty vodka bottle. The exact number of pills in the bottle is unknown, but the full bottle held as much as 50 capsules. The patient was unresponsive and had vomited, so her boyfriend called 911. On arrival to the emergency department, the patient is stuporous. Her vital signs are pulse 109 beats/min, respiratory rate 20 breaths/min, blood pressure 96/52, and oxygen saturation 95% on room air. Her examination shows mild nonspecific abdominal pain with palpation. The liver is not enlarged. Her initial laboratory values show a normal complete blood count, normal electrolytes, and kidney function. The aspartate aminotransferase is 68 IU/L, alanine aminotransferase is 46 IU/L, alkaline phosphatase is 110 IU/L, and total bilirubin is 1.2 mg/dL. Glucose and coagulation studies are normal. The serum alcohol level is 210 g/dL. The acetaminophen level is 350 μg/mL. What is the most appropriate next step in the treatment of this patient?

A. Administration of activated charcoal or cholestyramine
B. Administration of N-acetylcysteine 140 mg/kg followed by 70 mg/kg every 4 hours for a total of 15–20 doses
C. Continued monitoring of liver function, glucose, and coagulation studies every 4 hours with administration of N-acetylcysteine if these begin to change
D. Do nothing as normal liver function tests and coagulation studies are indicative of only a minor ingestion
E. Initiate hemodialysis for toxin clearance

VII-78. A 31-year-old health care worker is found to have a newly positive tuberculin skin test 6 weeks after an exposure to a patient with active pulmonary tuberculosis. He is asymptomatic and has a normal chest radiograph. Which of the following statements regarding initiation of isoniazid (INH) prophylactic therapy is true?

A. Acute hepatocellular injury due to INH is an idiosyncratic reaction that will manifest within the first 2 months of initiation of therapy.
B. Controlled trials have demonstrated that monthly monitoring of aminotransferase levels reduces morbidity in U.S. health care workers receiving INH prophylaxis.
C. Elevation of aminotransferase levels in the first 2 months of therapy is an indication to stop INH and switch to another drug.
D. The patient has a 50–70% chance of transient elevation of his aminotransferase levels in the first 2 months of treatment.
E. The frequency of acute hepatocellular injury due to INH is age dependent, increasing in patients >35 years of age.

VII-79. Which of the following statements is true about drug-induced liver injury (DILI)?

A. Direct toxic hepatitis is usually clinically indistinguishable from viral hepatitis.
B. Direct toxic hepatitis occurs with predictable regularity after exposure and is dose dependent.
C. "Idiosyncratic" drug reactions are easily identified by their histologic pattern on liver biopsy.
D. The incidence of DILI is higher in patients with chronic liver disease.
E. The occurrence of jaundice in a phase 3 clinical trial is not predictive of severe hepatotoxicity in postmarketing surveillance.

VII-80. Which of the following statements regarding drug-induced liver injury is true?

A. Amiodarone-induced liver injury resolves within days of stopping the drug.
B. Phenytoin-induced liver injury is only rarely accompanied by systemic symptoms and is usually picked up on screening liver enzyme testing.
C. Sodium valproate liver toxicity is more common in patients with mitochondrial deficiencies and can be ameliorated by the administration of IV carnitine.
D. The incidence of amoxicillin-induced liver injury is decreased when administered in combination with clavulanate.
E. When it occurs, nitrofurantoin liver toxicity happens soon after the initiation of the drug.

VII-81. A 38-year-old woman is evaluated for elevated transaminase levels that were identified during routine laboratory testing for life insurance. She is originally from Thailand and immigrated to the United States 10 years previously. She has been married to an American for the past 12 years, meeting him while he was living abroad for business. She previously worked in Thailand as a deputy tourism minister for the government but is not currently employed. She has no significant past medical history. She had one uncomplicated pregnancy at the age of 22. When queried about risk factors for liver disease, she denies alcohol intake or drug abuse. She has never had a blood transfusion. She recalls an episode of jaundice that she did not seek evaluation for about 15 years ago as it resolved spontaneously. She currently feels well, and her husband wished to have her added to his life insurance policy. On physical examination there are no stigmata of chronic liver disease. Her laboratory studies reveal an aspartate aminotransferase of 346 IU/L, alanine aminotransferase of 412 IU/L, alkaline phosphatase of 98 IU/L, and total bilirubin 1.5 of mg/dL. Further workup includes the following viral studies: hepatitis A IgG positive, hepatitis B surface antigen positive, hepatitis B e antigen positive, anti-hepatitis B virus core IgG positive, and hepatitis C IgG negative. The hepatitis B virus DNA level is 4.8×10^4 IU/mL. Which of the following medications is indicated for this patient?

A. Acyclovir
B. Entecavir
C. Ritonavir
D. Simeprevir
E. No treatment is necessary

VII-82. A 46-year-old man is known to have chronic hepatitis C virus (HCV) infection. He is a former IV drug user for more than 20 years who has been abstinent from drug use for 1 year. He was treated for tricuspid valve endocarditis 3 years previously. He does not know when he acquired HCV. His laboratory studies show a positive HCV IgG antibody with a viral load of greater than 1 million copies. The virus is genotype 2. His aspartate aminotransferase is 82 IU/L, and his alanine aminotransferase is 74 IU/L. He undergoes liver biopsy, which demonstrates a moderate degree of bridging fibrosis. Which of the following is the most predictive of the development of cirrhosis?

A. Abnormal transaminases
B. Bridging fibrosis on liver biopsy
C. Genotype 2
D. History of bacterial endocarditis
E. History of IV drug use

VII-83. For the patient in described in question VII-82, which of the following statements is true about potential treatment options for his hepatitis C virus?

A. A liver biopsy should be performed to determine the appropriate treatment regimen.
B. Combination therapy with sofosbuvir and velpatasvir would be a reasonable first-line treatment based on his genotype.
C. He should be treated with ribavirin and pegylated interferon as first-line agents.
D. Monotherapy with boceprevir would avoid any potential interactions with the CYP3A4 pathway.
E. Because his alanine aminotransferase and aspartate aminotransferase are not more than three times the upper limit of normal he does not currently require treatment.

VII-84. A 34-year-old woman is evaluated for fatigue, malaise, arthralgias, and a 10-lb weight loss over the past 6–8 weeks. She has no past medical history. Since feeling poorly, she has taken approximately one or two tablets of acetaminophen 500 mg daily. On physical examination, her temperature is 37.9°F (100.2°F), respiratory rate is 18 breaths/min, blood pressure is 100/48, heart rate is 92 beats/min, and oxygen saturation is 96% on room air. She has scleral icterus. Her liver edge is palpable 3 cm below the right costal margin. It is smooth and tender. The spleen is not enlarged. She has mild synovitis in the small joints of her hands. Her aspartate aminotransferase is 542 IU/L, alanine aminotransferase is 657 IU/L, alkaline phosphatase is 102 IU/L, total bilirubin is 5.3 mg/dL, and direct bilirubin is 4.8 mg/dL. Which of the following tests would be LEAST likely to be positive in this diagnosis?

A. Antinuclear antibodies in a homogeneous pattern
B. Anti-liver/kidney microsomal antibodies
C. Antimitochondrial antibodies
D. Hypergammaglobulinemia
E. Rheumatoid factor

VII-85. Which of the following statements is true about the mechanism of liver injury in patients with autoimmune hepatitis?

A. Acute viral hepatitis has not been associated with the subsequent development of autoimmune hepatitis.
B. Circulating autoantibodies in patients have been directly linked to hepatocyte injury.
C. Immune complex deposition is an important mechanism of hepatocyte injury.
D. Macrophages are the main effector cell of liver injury.
E. Molecular mimicry by cross-reacting antigens that contain epitopes similar to liver antigens is postulated to activate cytotoxic T cells.

VII-86. All of the following statements regarding alcoholic liver disease are true EXCEPT:

A. Fatty liver is present in >90% of daily and binge drinkers.
B. Hepatitis C infection worsens the prognosis of alcoholic liver disease.
C. Over 50% of alcoholics will develop alcoholic hepatitis.
D. Quantity and duration of alcohol consumption are the most important risk factors for the development of alcoholic liver disease.
E. The pathologic hallmarks of alcoholic liver disease are fatty liver, hepatitis, and cirrhosis.

VII-87. A 32-year-old woman is admitted to the hospital with fever, abdominal pain, and jaundice. She drinks approximately 6 beers daily and has recently increased her alcohol intake to more than 12 beers daily. She has no other substance abuse history and has no prior history of alcoholic liver disease or pancreatitis. She is not taking any medications. On physical examination, she appears ill and disheveled with a fruity odor to her breath. Her vital signs are heart rate 122 beats/min, blood pressure 95/56, respiratory rate 22 breaths/min, temperature 38.4°C (101.2°F), and oxygen saturation 98% on room air. She has scleral icterus, and spider angiomata are present on the trunk. The liver edge is palpable 10 cm below the right costal margin. The liver is smooth and tender to palpation. The spleen is not palpable. No ascites or lower extremity edema is present. Laboratory studies demonstrate an aspartate aminotransferase of 431 IU/L, alanine aminotransferase of 198 IU/L, bilirubin of 8.6 mg/dL, alkaline phosphatase of 201 IU/L, amylase of 88 U/L, and lipase of 50 U/L. Total protein is 6.2 g/dL, and albumin is 2.8 g/dL. The prothrombin time is 29 seconds (control, 13 seconds) with international normalized ratio of 2.2. What is the best approach to treatment of this patient?

A. Administer IV fluids, thiamine, and folate and observe for improvement in laboratory tests and clinical condition.
B. Administer IV fluids, thiamine, folate, and imipenem while awaiting blood culture results.
C. Administer prednisone 40 mg daily for 4 weeks before beginning a taper.
D. Consult surgery for management of acute cholecystitis.
E. Perform an abdominal CT with IV contrast to assess for necrotizing pancreatitis.

VII-88. Which of the following is true about the pathophysiology of alcoholic liver disease?

A. Alcoholic fatty liver disease is a benign condition and does not lead to lasting liver injury.
B. Alcoholic fatty liver disease is characterized by ballooning degeneration, spotty necrosis, polymorphonuclear infiltrate, and fibrosis in the perivenular and perisinusoidal space of Disse.
C. Fatty accumulation begins in the perivenular hepatocytes and can eventually involve the entire hepatic lobule.
D. It is relatively easy to differentiate alcoholic from nonalcoholic fatty liver disease on liver biopsy.
E. Once fatty accumulation occurs in the liver, it is not reversible.

VII-89. A 44-year-old man seeks evaluation for an abnormal finding on abdominal ultrasonography. He has a history of type 2 diabetes mellitus and is on insulin therapy. Last week, he was evaluated in the emergency department for mid-epigastric pain likely due to nonsteroidal anti-inflammatory drug therapy for muscle aches (he recently started exercising because his wife told him to lose weight). During the evaluation, an abdominal ultrasound showed marked fatty infiltration of the liver. Laboratory studies show his transaminases are 2× normal with normal alkaline phosphatase, bilirubin, and prothrombin time. Other than insulin, he takes no medications, does not consume alcohol or illicit drugs, and has no family history of liver disease. On physical examination, he is obese (body mass index 32 kg/m^2) with normal vital signs and no other abnormalities. You think he likely has nonalcoholic fatty liver disease (NAFLD). All of the following statements regarding his potential therapy are true EXCEPT:

A. Bariatric surgery is safe in patients with NAFLD.
B. Exercise may reduce hepatic steatosis.
C. Statins may worsen inflammation in NAFLD.
D. There are no therapies approved by the Food and Drug Administration for NAFLD.
E. Vitamin E may reduce aminotransferase levels and hepatic steatosis.

VII-90. Which of the following statements about nonalcoholic steatohepatitis (NASH) is true?

A. Insulin resistance is an important driver of lipid uptake, fat synthesis, and fat storage that leads to triglyceride accumulation in hepatocytes.
B. Greater than 50% of patients with nonalcoholic fatty liver disease (NAFLD) also have some component of NASH.
C. Serum biomarkers are useful in distinguishing NAFLD from NASH.
D. The contribution of NASH to the development of cirrhosis is on the decline in the United States.
E. Triglyceride accumulation within hepatocytes is directly cytotoxic.

VII-91. A 63-year-old man with cirrhosis and portal hypertension due to hemochromatosis presents with altered mental status. He has chronic ascites controlled with diet and spironolactone. He has a history of one esophageal bleed but none since starting propranolol. His family reports that over the last 2 days, he has become more confused, but he has had no melena or hematemesis. He is afebrile with normal vital signs, and physical examination is notable for ascites, asterixis, and being oriented only to person. His laboratory examination is notable for a hemoglobin of 10.1 g/dL (baseline 9.5), creatinine of 1.4 mg/dL (baseline 1.4), and blood urea nitrogen of 45 mg/dL (baseline 18). A paracentesis is performed that yields reveals clear fluid with 800 white blood cells/μL (40% neutrophils). Which of the following is the most indicated therapy?

A. Ampicillin, ceftriaxone, vancomycin
B. Cefotaxime
C. Esophagogastroduodenoscopy with banding
D. Hemodialysis
E. Lactulose

VII-92. A 48-year-old woman presents complaining of fatigue and itching. She has been tired for the past 6 months and recently has developed itching diffusely. It is worse in the evening hours but is intermittent. She does not note it to be worse following hot baths or showers. Her past medical history is significant only for hypothyroidism for which she takes levothyroxine 125 μg daily. On physical examination, she has mild jaundice and scleral icterus. The liver is enlarged to 15 cm on palpation and is palpable 5 cm below the right costal margin. Xanthomas are seen on both elbows. Hyperpigmentation is noticeable on the trunk and arms where the patient has excoriations. Laboratory studies demonstrate the following: white blood cells 8900/μL, hemoglobin 13.3 g/dL, hematocrit 41.6%, and platelets 160,000/μL. The creatinine is 1.2 mg/dL. The aspartate aminotransferase is 52 IU/L, alanine aminotransferase is 62 IU/L, alkaline phosphatase is 216 IU/L, total bilirubin is 3.2 mg/dL, and direct bilirubin is 2.9 mg/dL. The total protein is 8.2 g/dL, and albumin is 3.9 U/L. The thyroid-stimulating hormone is 4.5 U/mL. Antimitochondrial antibodies are positive. Perinuclear antineutrophil cytoplasmic antibodies (ANCA) and cytoplasmic ANCA are negative. What is the most likely cause of the patient's symptoms?

A. Lymphoma
B. Polycythemia vera
C. Primary biliary cirrhosis
D. Primary sclerosis cholangitis
E. Uncontrolled hypothyroidism

VII-93. A 42-year-old man with cirrhosis related to hepatitis C and alcohol abuse has ascites requiring frequent large-volume paracentesis. All of the following therapies would be indicated for this patient EXCEPT:

A. Fluid restriction to less than 2 L daily
B. Furosemide 40 mg daily
C. Sodium restriction to less than 2 g daily
D. Spironolactone 100 mg daily
E. Transjugular intrahepatic portosystemic shunt if medical therapy fails

VII-94. You are asked to consult on a 62-year-old white woman with pruritus for 4 months. She has noted progressive fatigue and a 5-lb weight loss. She has intermittent nausea but no vomiting and denies changes in her bowel habits. There is no history of prior alcohol use, blood transfusions, or illicit drug use. The patient is widowed and had two heterosexual partners in her lifetime. Her past medical history is significant only for hypothyroidism, for which she takes levothyroxine. Her family history is unremarkable. On examination, she is mildly icteric. She has spider angiomata on her torso. You palpate a nodular liver edge 2 cm below the right costal margin. The remainder of the examination is unremarkable. A right upper quadrant ultrasound confirms your suspicion of cirrhosis. You order a complete blood count and a comprehensive metabolic panel. What is the most appropriate next test?

A. 24-Hour urine copper
B. Antimitochondrial antibodies
C. Endoscopic retrograde cholangiopancreatography
D. Hepatitis B serologies
E. Serum ferritin

VII-95. A 55-year-old man with cirrhosis thought secondary to nonalcoholic steatohepatitis presents with altered mental status. All of the following can precipitate hepatic encephalopathy in this type of patient EXCEPT:

A. Dehydration
B. Hyperkalemia
C. Hypokalemia
D. Medication nonadherence
E. Spontaneous bacterial peritonitis

VII-96. A 64-year-old man with known cirrhosis is admitted to the intensive care unit with a large gastrointestinal bleed and altered mental status. He is confused and unable to provide any history. His initial hemoglobin is 6.9 g/dL, and his vital signs are notable for a heart rate of 115 beats/min and a blood pressure of 90/55. In addition to fluid resuscitation including transfusion of packed red blood cells, all of the following are appropriate therapy at this time EXCEPT:

A. Endoscopic sclerotherapy
B. Endoscopic variceal ligation
C. Octreotide
D. Propranolol
E. Transjugular intrahepatic portosystemic shunt

VII-97. In the patient in question VII-96, all of the following could be used as prophylaxis for further variceal bleeding EXCEPT:

A. Initiation of a nonselective beta blocker such as propranolol
B. Initiation of daily subcutaneous octreotide injections
C. Liver transplantation
D. Repeated variceal ligation if the initial bleed was controlled with endoscopic variceal ligation
E. Transjugular intrahepatic portosystemic shunt

VII-98. Which of the following statements is true about alcoholic cirrhosis?

A. Alcoholic cirrhosis is characterized by predominantly large (>2 cm) nodules in the liver.
B. If patients with alcoholic cirrhosis are able to stop drinking alcohol, their 5-year survival improves.
C. It is the most common cause of cirrhosis in the United States.
D. Parenterally administered tumor necrosis factor inhibitors have emerged as an important treatment option that can reduce mortality in patients with alcoholic cirrhosis.

VII-99. A 63-year-old female with primary biliary cirrhosis has refractory ascites that is managed with serial large volume paracentesis. She presents to the emergency department the night after an outpatient large volume tap with altered mental status. On arrival her laboratory studies are notable for a serum creatinine of 2.7 mg/dL (baseline 0.9 2 weeks ago) and a serum sodium of 127 mEq/L. Her urine output is low. You suspect possible hepatorenal syndrome. All of the following would be potential next steps in her evaluation and management EXCEPT:

A. Administer IV albumin to restore effective circulating volume
B. Look for alternative causes of renal failure
C. Referral for liver transplantation if creatinine continues to worsen
D. Start furosemide and spironolactone to increase her urine output
E. Start midodrine and octreotide to try to reduce splanchnic vasodilation and improve renal perfusion

VII-100. Which of the following patients is the highest priority for liver transplantation?

A. A 24-year-old woman with cirrhosis due to autoimmune hepatitis; she has been on the transplant list for 2 months and now has an elevated bilirubin, international normalized ratio (INR), and creatinine.
B. A 38-year-old woman with chronic hepatitis C and normal bilirubin and INR.
C. A 49-year-old man with alcoholic cirrhosis who has been on the transplant list for 6 months; he has had two esophageal variceal bleeds.
D. A 59-year-old man with a history of hyperlipidemia who was admitted to the intensive care unit 2 days ago with fulminant hepatic failure due to mistakenly ingesting *Amanita* mushrooms from his lawn.
E. A 64-year-old woman with primary hepatocellular carcinoma admitted to the hospital with acute renal failure.

VII-101. Which of the following statements regarding liver transplantation is true?

A. ABO incompatibility is an absolute contraindication to transplant.
B. Hepatocellular carcinoma is one of several conditions that receive disease-specific model for end-stage liver disease exceptions.
C. HIV infection is a contraindication to transplant.
D. Living donor transplants pose very little risk to the donor.
E. Preformed cytotoxic human leukocyte antigen antibodies are a contraindication to transplantation.

VII-102. A 44-year-old woman is evaluated for complaints of abdominal pain. She describes the pain as a postprandial burning pain. It is worse with spicy or fatty foods and is relieved with antacids. She is diagnosed with a gastric ulcer and is treated appropriately for *Helicobacter pylori*. During the course of her evaluation for her abdominal pain, the patient had a right upper quadrant ultrasound that demonstrated the presence of gallstones. Following treatment of *H. pylori*, her symptoms have resolved. She is requesting your opinion regarding whether treatment is required for the finding of gallstone disease. On review of the ultrasound report, there were numerous stones in the gallbladder, including in the neck of the gallbladder. The largest stone measures 2.8 cm. What is your advice to the patient regarding the risk of complications and the need for definitive treatment?

A. Given the size and number of stones, prophylactic cholecystectomy is recommended.
B. No treatment is necessary unless the patient develops symptoms of biliary colic frequent severe enough to interfere with the patient's life.
C. The only reason to proceed with cholecystectomy is the development of gallstone pancreatitis or cholangitis.
D. The risk of developing acute cholecystitis is about 5–10% per year.
E. Ursodeoxycholic acid should be given at a dose of 10–15 mg/kg daily for a minimum of 6 months to dissolve the stones.

VII-103. A 62-year-old man has been hospitalized in intensive care for the past 3 weeks following an automobile accident resulting in multiple long bone fractures and acute respiratory distress syndrome. He has been slowly improving but remains on mechanical ventilation. He is now febrile and hypotensive requiring vasopressors. He is being treated empirically with cefepime and vancomycin. Multiple blood cultures are negative. He has no new infiltrates or increasing secretions on chest radiograph. His laboratory studies demonstrated a rise in his liver function tests, bilirubin, and alkaline phosphatase. Amylase and lipase are normal. A right upper quadrant ultrasound shows sludge in the gallbladder but no stones. The bile duct is not dilated. What is the next best step in the evaluation and treatment of this patient?

A. Discontinue cefepime
B. Initiate treatment with clindamycin
C. Initiate treatment with metronidazole
D. Perform hepatobiliary scintigraphy
E. Refer for exploratory laparotomy

VII-104. A 41-year-old woman presents to your clinic with a week of jaundice. She notes pruritus, icterus, and dark urine. She denies fever, abdominal pain, or weight loss. The examination is unremarkable except for yellow discoloration of the skin. Total bilirubin is 6.0 mg/dL, and direct bilirubin is 5.1 mg/dL. Aspartate aminotransferase is 84 IU/L, alanine aminotransferase is 92 IU/L, and alkaline phosphatase is 662 IU/L. CT scan of the abdomen is unremarkable. Right upper quadrant ultrasound shows a normal gallbladder but does not visualize the common bile duct. What is the most appropriate next management step?

A. Antibiotics and observation
B. Endoscopic retrograde cholangiopancreatography
C. Hepatitis serologies
D. Hepatobiliary iminodiacetic acid scan
E. Serologies for antimitochondrial antibodies

VII-105. All of the following are contributing factors to cholesterol stone formation EXCEPT:

A. An excess of biliary cholesterol in relation to bile acids and phospholipids
B. Increased biliary secretion of cholesterol
C. Gallbladder hypomotility
D. Nucleation of cholesterol monohydrate crystals
E. Rapid weight gain through a high-fat diet

VII-106. A previously healthy 46-year-old female presents with 12 hours of right upper quadrant pain and nausea. The pain occasionally radiates to her right scapula. She has exquisite right upper quadrant tenderness on deep palpation. Laboratory studies show a mild elevation in her serum alkaline phosphatase. A right upper quadrant ultrasound shows stones in the bladder and a thickened gallbladder wall consistent with acute calculous cholecystitis. All of the following statements about cholecystectomy are true EXCEPT:

A. Five to ten percent of patients who undergo elective cholecystectomy develop diarrhea.
B. Atelectasis and subphrenic abscesses may occur after cholecystectomy.
C. Cholecystectomy provides near total relief of symptoms in up to 75–90% of patients.
D. The complication rate is higher in patients who undergo early cholecystectomy as opposed to delayed cholecystectomy (>6 weeks).
E. Undetected common bile duct stones are left behind in 1–5% of patients.

VII-107. A 46-year-old woman presents with a 1-week history of right upper quadrant pain, intermittent fever, and nausea. Her initial labs are notable for a markedly elevated bilirubin, mild elevations in her transaminases, and a modest elevation in her alkaline phosphatase. Ultrasound shows no gallstones. Magnetic resonance cholangiopancreatography reveals a beaded appearance of her intrahepatic and extrahepatic bile ducts due to multiple discrete strictures. Which of the following lab tests would be most helpful in understanding the cause of her current disease?

A. Hepatitis C antibody
B. Procalcitonin
C. Serum IgG-4 levels
D. Serum triglycerides
E. Urine histoplasma antigen

VII-108. All of the following disorders may be associated with a rise in serum amylase levels EXCEPT:

A. Esophageal carcinoma
B. Intestinal obstruction
C. Mumps
D. Pregnancy
E. Renal Failure

VII-109. Which of the following statements about imaging of the pancreas is true?

A. Abdominal CT has no role in the diagnosis of acute pancreatitis.
B. Endoscopic ultrasound (EUS) and magnetic resonance cholangiopancreatography have largely replaced endoscopic retrograde cholangiopancreatography in the diagnostic evaluation of pancreatic disease.
C. EUS is not helpful in the diagnosis of chronic pancreatitis.
D. Plane radiographs of the abdomen are commonly used in the evaluation of acute and chronic pancreatitis.
E. One advantage of pancreatic ultrasound is that intestinal bowel gas does not interfere with the ability to obtain images.

VII-110. Which of the following statements regarding pancreatic enzyme secretion is true?

A. Acetylcholine is an important neurotransmitter that stimulates pancreatic enzyme secretion.
B. All pancreatic enzymes have pH optima in the acidic range.
C. All pancreatic enzymes are secreted in their active forms.
D. Cholecystokinin receptors on human pancreatic acinar cells are important in pancreatic enzyme secretion.
E. Enterokinase found in the duodenal mucosa activates vasoactive intestinal peptide which then cleaves zymogens into active proteases.

VII-111. A 45-year-old woman with a known history of cholelithiasis is admitted to the hospital with severe mid-epigastric pain, fever to 38.5°C (101.3°F), tachycardia to 110 beats/min, and a blood pressure of 100/50. Her examination shows a diffusely tender abdomen with guarding. Radiographs show an abdominal ileus with no free air. Labs are notable for a hemoglobin of 15 g/dL and elevations of amylase and lipase. Which of the following statements regarding this patient's likely diagnosis is true?

A. Elevated lipase is more specific than elevated amylase for the diagnosis of acute pancreatitis.
B. Hypercalcemia occurs in >75% of cases of acute pancreatitis.
C. Magnitude of lipase elevation above normal is correlated with the severity of acute pancreatitis.
D. Serum amylase levels will remain elevated for up to 30 days after the resolution of acute pancreatitis.
E. The combination of elevated serum amylase and metabolic acidosis (pH <7.32) has a >90% positive predictive value for acute pancreatitis.

VII-112. A 27-year-old woman is admitted to the hospital with acute-onset severe right upper quadrant pain that radiates to the back. The pain is constant and not relieved with eating or bowel movements. Her labs show marked elevation in amylase and lipase, and acute pancreatitis is diagnosed. Which of the following is the best first test to demonstrate the etiology of her pancreatitis?

A. Right upper quadrant ultrasound
B. Serum alcohol level
C. Serum triglyceride level
D. Technetium hepatobiliary iminodiacetic acid scan
E. Urine drug screen

VII-113. A 58-year-old female with known alcohol abuse to the hospital with abdominal pain after a drinking binge. Her symptoms have been present for 3 days, and she has persisted to drink heavily. She now has persistent vomiting and feels dizzy on standing. On examination, she has severe epigastric and right upper quadrant tenderness and decreased bowel sounds, and she appears uncomfortable. She has a blue-red discoloration of the flanks bilaterally but denies any recent trauma. What is the significance of this finding?

A. Abdominal plain film is likely to show pancreatic calcification.
B. CT of the abdomen is likely to show severe necrotizing pancreatitis with hemoperitoneum.
C. Endoscopic ultrasound is likely to reveal a pancreatic mass.
D. Right upper quadrant ultrasound will likely show acute cholecystitis.
E. Transvaginal ultrasound will likely show a ruptured ectopic pregnancy.

VII-114. A 42-year-old male is admitted with severe epigastric pain radiating to the back. You suspect acute pancreatitis. All of the following are accepted diagnostic criteria for acute pancreatitis EXCEPT:

A. Confirmatory findings of acute pancreatitis on cross-sectional abdominal imaging
B. PaO_2 <60
C. Threefold or greater elevation in serum lipase and/or amylase
D. Typical abdominal pain in the epigastrium that may radiate to the back

VII-115. A 45-year-old female with known gallstones presents to the hospital with 2 days of mid-epigastric tenderness radiating to her back, as well as nausea and vomiting. Her serum lipase is elevated to four times the upper limit of normal and abdominal ultrasound reveals gallstones and findings consistent with acute pancreatitis. Her initial hematocrit is 48 and her vital signs are notable for sinus tachycardia with a pulse of 110 beats/min and a fever up to 38.1°C (100.6°F). After receiving 3 L of IV lactated ringers solution over the first 24 hours, her hematocrit drops to 38. Her heart rate and temperature have also improved. What is the significance of the drop in hematocrit?

A. Current fluid management should be continued as her drop in hematocrit is evidence of effective fluid resuscitation.
B. She has likely developed hemorrhage from severe necrotizing pancreatitis and should undergo urgent CT scanning of the abdomen.
C. She should be evaluated for hemolysis as a cause of the drop in hematocrit.
D. She should receive two units of packed red blood cells to prevent organ dysfunction from hypoperfusion related to evolving anemia.
E. She should undergo endoscopic ultrasound to look for an evolving pancreatic pseudocyst.

VII-116. A 56-year-old male presents to the emergency department with 1–2 days of worsening abdominal pain, fever, tachycardia and shortness of breath. He denies any alcohol use and has no known history of gallstones. His initial labs are notable for a markedly elevated amylase and lipase. He is given 2 L of IV isotonic fluids and is started on empiric antibiotics. CT of the chest, abdomen, and pelvis reveal severe necrotizing pancreatitis, as well as bilateral alveolar infiltrates with basilar atelectasis. He requires intubation and mechanical ventilation for evolving respiratory failure. All cultures are negative. Which of the following best explains the etiology of his respiratory failure?

A. He has developed acute respiratory distress syndrome (ARDS) from severe pancreatitis.
B. He has developed heart failure from overly aggressive fluid resuscitation.
C. He has developed pulmonary hemorrhage related to coagulopathy from sepsis.
D. He likely has culture-negative pneumonia and developed ARDS from direct lung injury.
E. He likely has sepsis from necrotizing pancreatitis and developed ARDS from the resulting bacteremia.

VII-117. Which of the following statements regarding enteral feeding in acute pancreatitis is true?

A. A patient with persistent evidence of pancreatic necrosis on CT 2 weeks after acute presentation should be maintained on bowel rest.
B. All patients with elevations of amylase and lipase and CT evidence of pancreatitis should be fasted until amylase and lipase normalize.
C. Enteral feeding has been demonstrated to have fewer infectious complications than total parenteral

nutrition in the management of patients with acute pancreatitis.

D. Patients requiring surgical removal of infected pancreatic pseudocysts should be treated with total parenteral nutrition.

E. Total parenteral nutrition has been shown to maintain integrity of the intestinal tract in acute pancreatitis.

VII-118. A 25-year-old woman with cystic fibrosis is diagnosed with chronic pancreatitis. She is at risk for all of the following complications EXCEPT:

A. Vitamin B_{12} deficiency
B. Vitamin A deficiency
C. Pancreatic carcinoma
D. Niacin deficiency
E. Steatorrhea

ANSWERS

VII-1. **The answer is E.** *(Chap. 314)* The colon is primarily responsible for stool dehydration, decreasing volumes from 1000–1500 mL to 100–200 mL. The stomach triturates and mixes the food bolus with pepsin and acid. The stomach also secretes intrinsic factor, which is necessary for vitamin B_{12} absorption. Gastric acid sterilizes the upper gut. Pancreatic juice contains enzymes for carbohydrate, protein, and fat digestion as well as bicarbonate to optimize the pH for enzyme activation.

VII-2. **The answer is C.** *(Chap. 314)* Pernicious anemia is associated with little or no gastric acid due to a lack of intrinsic factor. This is caused by autoantibodies that damage the gastric parietal cells. Gastrin G-cell hyperplasia results in increased gastrin levels, which leads to gastric acid hypersecretion. About 50% of G-cell hyperplasia is related to *Helicobacter pylori* infection and can be treated with eradication of the bacterium. Retained antrum syndrome is a rare postgastrectomy syndrome following a Billroth-II procedure in which the antrum has not been entirely removed. Some patients with duodenal ulcers have acid hypersecretion. Zollinger-Ellison syndrome is caused by a tumor (usually in the pancreas or duodenum) that secretes gastrin and therefore causes gastric acid hypersecretion.

VII-3. **The answer is D.** *(Chap. 314)* Mesenteric ischemia, biliary colic, and neoplasms most commonly cause noninflammatory visceral pain. Peptic ulcer, appendicitis, diverticulitis, inflammatory bowel disease, pancreatitis, cholecystitis, and infectious enterocolitis are all painful inflammatory diseases.

VII-4. **The answer is A.** *(Chap. 314)* Diarrhea from malabsorption usually improves with fasting, whereas secretory diarrhea persists without oral intake. Sudden awakening from sound sleep by pain suggests organic rather than functional disease. Symptoms from mechanical obstruction, ischemia, inflammatory bowel disease, and functional bowel disorders are worsened by meals. Ulcer pain occurs intermittently over weeks to months, whereas biliary colic has a sudden onset and lasts up to several hours. Ulcer symptoms may be relieved by eating or antacids.

VII-5. **The answer is B.** *(Chap. 315)* Since this patient is over 50 years old, even without a family history, screening for colorectal cancer is recommended. Colonoscopy is the gold standard for imaging the colonic mucosa. The cecum is reached in >95% of cases and the terminal ileum can often be examined. Colonoscopy has greater sensitivity than barium enema for colitis, polyps, and cancer. CT colonography rivals the accuracy of colonoscopy for detection of some polyps and cancer, although it is not as sensitive for the detection of flat lesions, such as serrated polyps. Flexible sigmoidoscopy is similar to colonoscopy, but it visualizes only the rectum and a variable portion of the left colon, typically to 60 cm from the anal verge.

VII-6. **The answer is E.** *(Chap. 315)* Patients undergoing percutaneous endoscopic gastrostomy tube placement should receive prophylactic antibiotics at the time as the procedure to prevent peristomal infection. Table VII-6 lists common endoscopic procedures and whether or not antibiotic prophylaxis is indicated.

TABLE VII-6 Antibiotic Prophylaxis for Endoscopic Procedures

Patient Condition	Procedure Contemplated	Goal of Prophylaxis	Periprocedural Antibiotic Prophylaxis
All cardiac conditions	Any endoscopic procedure	Prevention of infective endocarditis	Not indicated
Bile duct obstruction in the absence of cholangitis	ERCP with complete drainage	Prevention of cholangitis	Not recommended
Bile duct obstruction in absence of cholangitis	ERCP with anticipated incomplete drainage (e.g., sclerosing cholangitis, hilar strictures)	Prevention of cholangitis	Recommended; continue antibiotics after the procedure
Sterile pancreatic fluid collection (e.g., pseudocyst, necrosis), which communicates with pancreatic duct	ERCP	Prevention of cyst infection	Recommended; continue antibiotics after the procedure
Sterile pancreatic fluid collection	Transmural drainage	Prevention of cyst infection	Recommended
Solid lesion along upper GI tract	EUS-FNA	Prevention of local infection	Not recommended[a]
Solid lesion along lower GI tract	EUS-FNA	Prevention of local infection	Not recommended[a]
Cystic lesions along GI tract (including mediastinum and pancreas)	EUS-FNA	Prevention of cyst infection	Recommended
All patients	Percutaneous endoscopic feeding tube placement	Prevention of peristomal infection	Recommended[b]
Cirrhosis with acute GI bleeding	Required for all such patients, regardless of endoscopic procedures	Prevention of infectious complications and reduction of mortality	Recommended, on admission[c]
Continuous peritoneal dialysis	Lower GI tract endoscopy	Prevention of bacterial peritonitis	Recommended
Synthetic vascular graft and other nonvalvular cardiovascular devices	Any endoscopic procedure	Prevention of graft and device infection	Not recommended[d]
Prosthetic joints	Any endoscopic procedure	Prevention of septic arthritis	Not recommended[e]

[a] Low rates of bacteremia and local infection.

[b] Cefazolin or an antibiotic with equivalent coverage of oral and skin flora.

[c] Risk for bacterial infection associated with cirrhosis and GI bleeding is well established; ceftriaxone or a quinolone antibiotic recommended.

[d] No reported cases of infection associated with endoscopy.

[e] Very low risk of infection.

Abbreviations: ERCP, endoscopic retrograde cholangiopancreatography; EUS-FNA, endoscopic ultrasound–fine-needle aspiration; GI, gastrointestinal.

Source: Adapted with permission from ASGE Standards of Practice Committee et al: Antibiotic prophylaxis for GI endoscopy. *Gastrointest Endosc* 81:81, 2015.

VII-7. **The answer is E.** *(Chap. 315)* Severe pain in and of itself is not an indication for urgent endoscopy in the setting of an upper GI bleed. The severity of the initial hemorrhage is the most important indication for urgent endoscopy, since a large initial bleed increases the likelihood of ongoing or recurrent bleeding. Patients with resting hypotension or orthostatic change in vital signs, repeated hematemesis, bloody nasogastric aspirate that does not clear with large volume lavage, or those requiring blood transfusions should be considered for urgent endoscopy. In addition, patients with cirrhosis, coagulopathy, respiratory or renal failure, and those over 70 years of age are more likely to have significant rebleeding and to benefit from prompt evaluation and treatment. Perforation of the esophagus, stomach, or duodenum may cause acute severe pain in conjunction with upper GI bleeding. Upright chest/abdomen radiography or CT scanning may be indicated.

VII-8. **The answer is B.** *(Chap. 315)* The endoscopic appearance of peptic ulcers provides useful prognostic information and guides the need for endoscopic therapy in patients with acute hemorrhage. A clean-based ulcer is associated with a low risk (3–5%) of rebleeding; patients with melena and a clean-based ulcer are often discharged home from the emergency room or endoscopy suite if they are young, reliable, and otherwise healthy. Flat pigmented spots and adherent clots covering the ulcer base have a 10% and 20% risk of rebleeding, respectively. Endoscopic therapy may be considered for an ulcer with an adherent clot. When a fibrin plug is seen protruding from a vessel wall in the base of an ulcer (so-called sentinel clot or visible vessel), the risk of rebleeding from the ulcer is 40%. This finding generally leads to endoscopic therapy to decrease the rebleeding rate. When active spurting from an ulcer is seen, there is a 90% risk of ongoing bleeding without therapy.

VII-9. **The answer is A.** *(Chap. 315)* Endoscopy, also known as esophagogastroduodenoscopy, is the best test for evaluation of the proximal gastrointestinal tract. Because of high-quality images, disorders of color such as Barrett metaplasia and mucosal irregularities are easily demonstrated. Sensitivity of endoscopy is superior to that of barium radiography for mucosal lesions. Because the endoscope has an instrumentation channel, biopsy specimens are easily obtained, and dilation of strictures can also be performed. The sensitivity of radiography compared with endoscopy for detecting reflux esophagitis reportedly ranges from 22 to 95%, with higher grades of esophagitis (i.e., ulceration or stricture) exhibiting greater detection rates. Conversely, the sensitivity of barium radiography for detecting esophageal strictures is greater than that of endoscopy, especially when the study is done in conjunction with barium-soaked bread or a 13-mm barium tablet. Barium studies also provide an assessment of esophageal function and morphology that may be undetected on endoscopy. The major shortcoming of barium radiography is that it rarely obviates the need for endoscopy. Barium radiography does not require sedation, which in some populations at risk for conscious sedation is an important consideration.

VII-10. **The answer is E.** *(Chap. 316)* Intermittent solid food dysphagia is a classic symptom in Schatzki ring in which a distal esophageal ring occurs at the squamocolumnar mucosal junction. The origin of these rings is unknown, and smaller rings with a lumen of greater than 13 mm are common in the general population (up to 15%). When the lumen is less than 13 mm, dysphagia may occur. Schatzki rings typically occur in persons older than 40 years and often cause “steakhouse syndrome” from meat getting stuck at the ring. The rings are easily treated with dilation. Plummer-Vinson syndrome also includes esophageal rings, but typically, the rings occur in the proximal esophagus, are associated with iron-deficiency anemia, and occur in middle-aged women. Achalasia involves both solid and liquid dysphagia often with regurgitation. Adenocarcinoma often includes solid and liquid dysphagia at later stages. Most esophageal diverticula are asymptomatic.

VII-11. **The answer is A.** *(Chap. 316)* This patient has symptoms of esophagitis. In patients with HIV, various infections can cause esophagitis, including herpes simplex virus (HSV), cytomegalovirus (CMV), varicella-zoster virus, *Candida*, and HIV itself. The lack of thrush does not rule out *Candida* as a cause of esophagitis, and esophagogastroduodenoscopy (EGD) is necessary for diagnosis. CMV classically causes serpiginous ulcers in the distal esophagus that may coalesce to form large ulcers. Brushings alone are insufficient for diagnosis, and biopsies must be performed. Biopsies reveal intranuclear and intracytoplasmic inclusions with enlarged nuclei in large fibroblasts and endothelial cells. Given this patient’s notable swallowing symptoms, IV ganciclovir is the treatment of choice. Valganciclovir is an effective oral preparation. Foscarnet is useful in treating ganciclovir-resistant CMV. HSV manifests as vesicles and punched-out lesions in the esophagus with the characteristic findings on biopsy of ballooning degeneration with ground-glass changes in the nuclei. It can be treated with acyclovir or foscarnet in resistant cases. *Candida* esophagitis has the appearance of yellow nodular plaques with surrounding erythema. Treatment usually requires fluconazole therapy. Finally, HIV alone can cause esophagitis that can be quite resistant to therapy. On EGD, these ulcers appear deep and linear. Treatment with thalidomide or oral glucocorticoids is employed, and highly active antiretroviral therapy should be considered.

VII-12. **The answer is A.** *(Chap. 316)* The barium swallow image demonstrates achalasia with esophageal dilation narrowing at the gastroesophageal junction and an air-fluid level in the mid-esophagus. Achalasia is a rare disease caused by loss of ganglion cells within the esophageal myenteric plexus with a population incidence of about 1:100,000; it usually presents between age 25 and 60. With long-standing disease, aganglionosis is noted. The disease involves both excitatory (cholinergic) and inhibitory (nitric oxide) ganglionic neurons. This leads to impaired deglutitive lower esophageal sphincter (LES) relaxation and absent peristalsis. Increasing evidence suggests that the ultimate cause of ganglion cell degeneration in achalasia is an autoimmune process attributable to a latent infection with human herpes simplex virus 1 combined with genetic susceptibility. Long-standing achalasia is characterized by progressive dilatation and sigmoid deformity of the esophagus with hypertrophy of the LES. Clinical manifestations may include dysphagia, regurgitation, chest pain, and weight loss. Most patients report solid and liquid food dysphagia. Regurgitation occurs when food, fluid, and secretions are retained in the dilated esophagus. Patients with advanced achalasia are at risk for bronchitis, pneumonia, or lung abscess from chronic regurgitation and aspiration. The differential diagnosis of achalasia includes diffuse esophageal spasm, Chagas disease, and pseudo-achalasia. Chagas disease is endemic in areas of central Brazil, Venezuela, and northern Argentina and spread by the bite of the reduviid (kissing) bug that transmits the protozoan *Trypanosoma cruzi*. The chronic phase of the disease develops years after infection and results from destruction of autonomic ganglion cells throughout the body, including the heart, gut, urinary tract, and respiratory tract. Tumor infiltration, most commonly seen with carcinoma in the gastric fundus or distal esophagus, can mimic idiopathic achalasia. The resulting pseudo-achalasia accounts for up to 5% of suspected cases and is more likely with advanced age, abrupt onset of symptoms (<1 year), and weight loss. Hence, endoscopy is a necessary part of the evaluation of achalasia. When the clinical suspicion for pseudo-achalasia is high and endoscopy nondiagnostic, CT scanning or endoscopic ultrasound may be of value. There is no known way of preventing or reversing achalasia. Therapy is directed at reducing LES pressure so that gravity and esophageal pressurization promote esophageal emptying. Peristalsis rarely, if ever, recovers. Botulinum toxin, injected into the LES under endoscopic guidance, inhibits acetylcholine release from nerve endings and improves dysphagia in about 66% of cases for at least 6 months. The only durable therapies for achalasia are pneumatic dilatation and Heller myotomy.

VII-13. **The answer is B.** *(Chap. 316)* These findings are characteristic of Barrett metaplasia, the most serious complication of gastroesophageal reflux disease. Barrett metaplasia has a strong association with the subsequent development of esophageal adenocarcinoma. The incidence of these lesions has increased, not decreased, in the era of potent acid suppression. Barrett metaplasia is endoscopically recognized by tongues of reddish mucosa extending proximally from the gastroesophageal junction or histopathologically identified by the finding of specialized columnar metaplasia. Barrett metaplasia can progress to adenocarcinoma through the intermediate stages of low- and high-grade dysplasia. Due to this risk, areas of Barrett metaplasia and especially any included areas of mucosal irregularity should be extensively biopsied. No high-level evidence confirms that aggressive antisecretory therapy or antireflux surgery causes regression of Barrett esophagus or prevents adenocarcinoma. Although the management of Barrett esophagus remains controversial, the finding of dysplasia in Barrett esophagus, particularly high-grade dysplasia, mandates further intervention. In addition to the high rate of progression to adenocarcinoma, there is also a high prevalence of unrecognized coexisting cancer with high-grade dysplasia. Nonetheless, treatment remains controversial. Esophagectomy, intensive endoscopic surveillance, and mucosal ablation have all been advocated. Currently, esophagectomy is the gold standard treatment for high-grade dysplasia in an otherwise healthy patient with minimal surgical risk. However, esophagectomy has a mortality ranging from 3 to 10%, along with substantial morbidity. As a result of these factors and the increasing evidence of the effectiveness of endoscopic therapy with purpose-built radiofrequency ablation devices, many now favor this therapy as a preferable management strategy.

VII-14. **The answer is D.** *(Chap. 316)* This person has eosinophilic esophagitis (EoE) as evidenced by his symptoms, esophagogastroduodenoscopy appearance, and pathologic findings. The biopsy shows infiltration of the esophageal squamous epithelium with eosinophils, with basal cell hyperplasia, and lamina propria fibrosis. EoE characteristically exhibits multiple esophageal rings, linear furrows, white punctate exudate, and strictures on endoscopy. A trial of a proton pump inhibitor (PPI) leads to the resolution of eosinophilic esophagitis in about 30–50% of cases. If a PPI trial does not work, patients are often encouraged to start an elimination diet to try to avoid common food allergens that might be causative. Swallowed topical corticosteroids are effective but esophagitis often recurs on cessation of the topical steroid. Systemic corticosteroids are only used if all other treatment options fail. The role of newer anti–interleukin-5 therapies such as mepolizumab in treating eosinophilic esophagitis is not yet known.

VII-15. **The answer is A.** *(Chap. 316)* The symptoms and barium swallow are consistent with the diagnosis of diffuse esophageal spasm (DES), which is characterized by DES episodes of dysphagia and chest pain attributable to abnormal esophageal contractions with normal deglutitive LES relaxation. The barium swallow demonstrates the characteristic "corkscrew" esophagus results from spastic contraction of the helical muscle array in the esophageal wall. Manometry in patients with DES is characterized by contractions in the distal esophagus with short latency relative to the time of the pharyngeal contraction. However, DES may be confused with or actually overlap with some forms of achalasia. High-resolution manometry has led to the recognition of three distinct types of achalasia. All are characterized by impaired LES contraction and the absence of peristalsis. Classic achalasia has minimal pressurization of the esophageal body, whereas substantial fluid pressurization is observed in achalasia with esophageal compression, and spastic esophageal contractions are observed with spastic achalasia. DES may be particularly confused with spastic achalasia. Manometric studies of the esophagus performed to evaluate chest pain and/or dysphagia often report minor abnormalities (e.g., hypertensive or hypotensive peristalsis, hypertensive LES) that are insufficient to diagnose either achalasia or DES. These findings are of unclear significance.

VII-16. **The answer is D.** *(Chap. 316)* The side effects of proton pump inhibitor (PPI) therapy are generally minimal. Rare cases of interstitial nephritis and severe, reversible hypomagnesemia have been reported. Vitamin B_{12} and iron absorption may be compromised and susceptibility to enteric infections, particularly *Clostridium difficile* colitis, increased with treatment. PPIs are more effective than H_2 receptor antagonists, but both are more effective than placebo. The effectiveness of PPIs is not substantially increased at higher doses. The most broadly applicable recommendation for gastroesophageal reflux disease (GERD) treatment is weight reduction. Even though the benefit with respect to reflux cannot be assured, the strong epidemiologic relationship between body mass index and GERD and the secondary health gains of weight reduction is beyond dispute.

VII-17. **The answer is D.** *(Chap. 317)* Noninvasive testing for *Helicobacter pylori* infection is recommended in patients with suggestive symptoms and no other indication for endoscopy (e.g., gastrointestinal bleeding, atypical symptoms). Several tests have good sensitivity and specificity (Table VII-17), including plasma serology for *H. pylori*, 14C- or 13C-urea

TABLE VII-17 **Tests for Detection of *Helicobacter pylori***

Test	Sensitivity/Specificity (%)	Comments
Invasive (Endoscopy/Biopsy Required)		
Rapid urease	80–95/95–100	Simple, false negative with recent use of PPIs, antibiotics, or bismuth compounds
Histology	80–90/>95	Requires pathology processing and staining; provides histologic information
Culture	—/—	Time-consuming, expensive, dependent on experience; allows determination of antibiotic susceptibility
Noninvasive		
Serology	>80/>90	Inexpensive, convenient; not useful for early follow-up
Urea breath test	>90/>90	Simple, rapid; useful for early follow-up; false negatives with recent therapy (see rapid urease test); exposure to low-dose radiation with ^{14}C test
Stool antigen	>90/>90	Inexpensive, convenient

Abbreviation: PPIs, proton pump inhibitors.

breath test, and the fecal *H. pylori* antigen test. Sensitivity and specificity are >80% and >90%, respectively, for serology, whereas the sensitivity and specificity of the urea breath test and fecal antigen testing are >90% for both. Serology is not useful for early follow-up after therapy completion because antibody titers will take several weeks to months to fall. The urea breath test, which relies on the presence of urease secreted by *H. pylori* to digest the swallowed radioactive urea and liberate 14C or 13C as part of ammonia, is simple and rapid. It is useful for early follow-up because it requires living bacteria to secrete urease and produce a positive test. The limitations to the test include requirement for ingestion of radioactive materials, albeit low dose, and false-negative results with recent use of proton pump inhibitors, antibiotics, or bismuth compounds. Stool antigen testing is cheap and convenient but is not established for proof of eradication.

VII-18. **The answer is A.** *(Chap. 317)* Documented eradication of *Helicobacter pylori* in patients with peptic ulcer disease (PUD) is associated with a dramatic decrease in ulcer recurrence to <10–20% compared with 59% in gastric ulcer patients and 67% in duodenal ulcer patients when the organism is not eliminated. Eradication of the organism may lead to diminished recurrent ulcer bleeding. The effect of its eradication on ulcer perforation is unclear. Extensive effort has been made in determining who of the many individuals with *H. pylori* infection should be treated. The common conclusion arrived at by multiple consensus conferences around the world is that *H. pylori* should be eradicated in patients with documented PUD. This holds true independent of time of presentation (first episode or not), severity of symptoms, presence of confounding factors such as ingestion of nonsteroidal anti-inflammatory drugs, or whether the ulcer is in remission. Multiple drugs have been evaluated in the therapy of *H. pylori*. No single agent is effective in eradicating the organism. Combination therapy for 14 days provides the greatest efficacy, although regimens based on sequential administration of antibiotics also appear promising (Table VII-18). A shorter administration course (7–10 days), although attractive, has not proved as successful as the 14-day regimens. Suggested treatment regimens for *H. pylori* are outlined below. Choice of a particular regimen will be influenced by several factors, including efficacy, patient tolerance, existing antibiotic resistance, and cost of the drugs. The aim for initial eradication rates should be 85–90%. Dual therapy (proton pump inhibitor [PPI] plus amoxicillin, PPI plus clarithromycin, ranitidine bismuth citrate [Tritec] plus clarithromycin) is not recommended in view of studies demonstrating eradication rates of <80–85%. Addition of acid suppression assists in providing early symptom relief and enhances bacterial eradication. Triple therapy, although effective, has several drawbacks, including the potential for poor patient compliance and drug-induced side effects. Compliance is addressed by simplifying the regimens so that patients can take the medications twice a day. Simpler (dual therapy) and shorter regimens (7 and 10 days) are not as effective as triple therapy for 14 days. Two anti–*H. pylori* regimens are available in prepackaged formulation: Prevpac (lansoprazole, clarithromycin, and amoxicillin) and Helidac (bismuth subsalicylate, tetracycline, and metronidazole). The contents of the Prevpac are to be taken twice per day for 14 days, whereas Helidac constituents are taken four times per day with an antisecretory agent (PPI or H_2 blocker), also taken for at least 14 days. Clarithromycin-based triple therapy should be avoided in settings where *H. pylori* resistance to this agent exceeds 15–20%. Quadruple therapy should be reserved for patients with failure to eradicate *H. pylori* after an effective initial course.

VII-19. **The answer is C.** *(Chap. 317)* Fasting gastrin levels can be elevated in a variety of conditions, including atrophic gastritis with or without pernicious anemia, G-cell hyperplasia, and acid suppressive therapy (gastrin levels increase as a consequence of loss of negative feedback). The diagnostic concern in a patient with persistent ulcers following optimal therapy is Zollinger-Ellison syndrome (ZES). A fasting result is not sufficient to make a diagnosis because gastrin levels may be elevated in a variety of conditions. Elevated basal acid secretion also is consistent with ZES, but up to 12% of patients with peptic ulcer disease may have basal acid secretion as high as 15 mEq/h. Thus, additional testing is necessary. Gastrin levels may go up with a meal (>200%), but this test does not distinguish G-cell hyperfunction from ZES. The best test in this setting is the secretin stimulation test. An increase in gastrin levels >200 pg within 15 minutes of administering 2 μg/kg of

TABLE VII-18 Recommended First-Line Therapies for *Helicobacter pylori* Infection

Regimen	Drugs (doses)	Dosing Frequency	Duration (days)	FDA Approval
Clarithromycin triple	PPI (standard or double dose)	bid	14	Yes[a]
	Clarithromycin (500 mg)			
	Amoxicillin (1 g) or metronidazole (500 mg tid)			
Bismuth quadruple	PPI (standard dose)	bid	10–14	No[b]
	Bismuth subcitrate (120–300 mg) or subsalicylate (300 mg)	qid		
	Tetracycline (500 mg)	qid		
	Metronidazole (250–500 mg)	qid (250) tid to qid (500)		
Concomitant	PPI (standard dose)	bid	10–14	No
	Clarithromycin (500 mg)			
	Amoxicillin (1 g)			
	Nitroimidazole (500 mg)[c]			
Sequential	PPI (standard dose)	bid	5–7	No
	PPI, clarithromycin (500 mg) + nitroimidazole (500 mg)[c]	bid	5–7	
Hybrid	PPI (standard dose) + amoxicillin (1 g)	bid	7	No
	PPI, amoxicillin, clarithromycin (500 mg), nitroimidazole (500 mg)[C]	bid	7	
Levofloxacin triple	PPI (standard or double dose) + amoxicillin (1 g)	bid	5–7	No
	Levofloxacin (500 mg)	qd		
	Amoxicillin (1 g)	bid		
Levofloxacin sequential	PPI (standard or double dose) + amoxicillin (1 g)	bid	5–7	No
	PPI, amoxicillin, levofloxacin (500 mg qd), nitroimidazole (500 mg)[c]	bid	5–7	
LOAD	Levofloxacin (250 mg)	qd	7–10	No
	PPI (double dose)	qd		
	Nitazoxanide (500 mg)	bid		
	Doxycycline (100 mg)	qd		

[a] Several PPI, clarithromycin, and amoxicillin combinations have achieved FDA approval. PPI, clarithromycin, and metronidazole is not an FDA-approved treatment regimen.

[b] PPI, bismuth, tetracycline, and metronidazole combined with a PPI for 10 days is an FDA-approved treatment regimen.

[c] Metronidazole or tinidazole.

Abbreviations: bid, twice daily; FDA, Food and Drug Administration; PPI, proton pump inhibitor; tid, three times daily; qd, once daily; qid, four times daily.

Source: Reproduced with permission from Chey WD et al: ACG Clinical Guideline: treatment of *Helicobacter pylori* Infection. *Am J Gastroenterol* 112:212, 2017.

secretin by IV bolus has a sensitivity and specificity of >90% for ZES. Endoscopic ultrasonography is useful in locating the gastrin-secreting tumor once the positive secretin test is obtained. Genetic testing for mutations in the gene that encodes the menin protein can detect the fraction of patients with gastrinomas that are a manifestation of multiple endocrine neoplasia type 1 (Wermer syndrome). Gastrinoma is the second most common tumor in this syndrome after parathyroid adenoma, but its peak incidence is generally in the third decade.

VII-20. **The answer is B.** *(Chap. 317)* Long-term acid suppression, especially with proton pump inhibitors (PPIs), has been associated with a higher incidence of community-acquired pneumonia as well as community- and hospital-acquired *Clostridium difficile*–associated disease. The impact of PPI-induced changes in the host microbiome is postulated to play a role in the increased risk of infection, but this theory needs to be confirmed. Cimetidine, not famotidine, may have weak antiandrogenic side effects resulting in reversible gynecomastia and impotence, primarily in patients receiving high doses for prolonged periods of time (months to years). The long-term use of calcium carbonate (converts to calcium chloride in the stomach) can lead to milk-alkali syndrome (hypercalcemia, hyperphosphatemia with possible renal calcinosis and progression to renal insufficiency). Rebound gastric acid hypersecretion has been described in *Helicobacter pylori*–negative individuals after discontinuation of PPIs, not H_2 blockers. It occurs even after relatively short-term usage (2 months) and may last for up to 2 months after the PPI has been discontinued. The mechanism involves gastrin-induced hyperplasia and hypertrophy of histamine-secreting enterochromaffin-like cells. The clinical relevance of this observation is that individuals may have worsening symptoms of gastroesophageal reflux disease or dyspepsia on stopping the PPI. Gradual tapering of the PPI and switching to an H_2 receptor antagonist may prevent this from occurring. Aluminum hydroxide can produce constipation and phosphate depletion. Magnesium hydroxide can produce loose stools.

VII-21. **The answer is D.** *(Chap. 317)* Basal acid production occurs in a circadian pattern, with highest levels occurring during the night and lowest levels during the morning hours. Cholinergic input via the vagus nerve and histaminergic input from local gastric sources are the principal contributors to basal acid secretion. Stimulated gastric acid secretion occurs primarily in three phases based on the site where the signal originates (cephalic, gastric, and intestinal). Sight, smell, and taste of food are the components of the cephalic phase, which stimulates gastric secretion via the vagus nerve. The gastric phase is activated once food enters the stomach. This component of secretion is driven by nutrients (amino acids and amines) that directly (via peptone and amino acid receptors) and indirectly (via stimulation of intramural gastrin-releasing peptide neurons) stimulate the G cell to release gastrin, which in turn activates the parietal cell via direct and indirect mechanisms. Distention of the stomach wall also leads to gastrin release and acid production. The last phase of gastric acid secretion is initiated as food enters the intestine and is mediated by luminal distention and nutrient assimilation.

VII-22. **The answer is B.** *(Chap. 318)* The patient presents with nonspecific gastrointestinal symptoms, but the presence of weight loss does suggest malabsorption syndrome. Patients with lactose intolerance are usually able to relate symptoms to consumption of milk-based products and also report a strong history of crampy pain and flatulence. Therefore, a lactose-free diet is unlikely to be helpful. The patient does not have nocturnal diarrhea, which is commonly a feature of steatorrhea along with floating stools. In the absence of symptoms suggesting fat malabsorption, the first test should not be fecal fat measurement. Because the patient has weight loss, irritable bowel syndrome is less likely, and increased dietary fiber is unlikely to be useful. Finally, the patient's symptoms may be consistent with celiac disease. Antibodies to gliadin, endomysium, and tissue transglutaminase can be easily measured in peripheral blood. Antiendomysial antibody has 90–95% sensitivity and equal specificity, making it a reasonable first test in symptomatic individuals. The presence of the antibody is not diagnostic, however, and duodenal biopsy is recommended. Duodenal biopsy will show villous atrophy, absence or reduced height of villi, cuboidal appearance of surface epithelial cells, and increased lymphocytes and plasma cells in the lamina propria. These changes regress with complete removal of gluten from the diet.

VII-23. **The answer is E.** *(Chap. 318)* The patient presents with symptoms suggestive of Whipple disease, a chronic multisystem disease often including diarrhea/steatorrhea, migratory arthralgias, weight loss, and central nervous system (CNS) or cardiac problems. Generally the presentation is of insidious onset, and dementia is a late finding and a poor prognostic sign. The disease primarily occurs in middle-aged white males. The diagnosis requires small bowel biopsy and demonstration of periodic acid–Schiff-positive macrophages within the small bowel. Small bacilli are often present and suggest the diagnosis of Whipple disease. Similar macrophages may be found in other affected organs (e.g., the CNS). Dilated lymphatics are present in patients with intestinal lymphangiectasia. Mononuclear cell infiltrate in the lamina propria is often demonstrated in patients with tropical sprue, and fat villi with crypt hyperplasia is the hallmark of celiac disease.

VII-24. **The answer is D.** *(Chap. 318)* This patient has a stool osmolality gap (measured stool osmolality – calculated stool osmolality) of 10 mOsm/L, suggesting a secretory rather than an osmotic cause for diarrhea. Secretory causes of diarrhea include toxin-mediated diarrhea (cholera, enterotoxigenic *Escherichia coli*) and intestinal peptide–mediated diarrhea in which the major pathophysiology is a luminal or circulating secretagogue. The distinction between secretory diarrhea and osmotic diarrhea aids in forming a differential diagnosis. Secretory diarrhea will not decrease substantially during a fast and has a low osmolality gap. Osmotic diarrhea will generally decrease during a fast and has a high (>50 mOsm/L) osmolality gap. Celiac sprue, chronic pancreatitis, lactase deficiency, and Whipple disease all cause osmotic diarrhea. A low stool osmolality (<290 mOsm/kg H_2O) reflects the addition of either dilute urine or water, indicating either collection of urine and stool together or so-called factitious diarrhea, a form of Munchausen syndrome.

VII-25. **The answer is D.** *(Chap. 318)* The intestine is exposed to a large number of potential antigens and enteric and invasive microorganisms, and it is extremely active at preventing the entry of almost all of these agents. The intestinal mucosa also synthesizes and secretes secretory IgA. The intestine absorbs ~7–8 L of fluid daily, a volume comprising dietary fluid intake (1–2 L/d) and salivary, gastric, pancreatic, biliary, and intestinal fluid (6–7L/d). Several stimuli, especially bacteria and bacterial enterotoxins, induce fluid and electrolyte secretion that may lead to diarrhea. The intestinal mucosa is a major site for the production of proteins, including apolipoproteins. The intestine is one of the largest endocrine organs in the body and produces several amines (e.g., 5-hydroxytryptophan) and peptides that serve as paracrine and hormonal mediators of intestinal function. Bile acids are not present in the diet but are synthesized in the liver by a series of enzymatic steps that also represent cholesterol catabolism. Bile acids are either primary or secondary. Primary bile acids are synthesized in the liver from cholesterol, and secondary bile acids are synthesized from primary bile acids in the intestine by colonic bacterial enzymes.

VII-26. **The answer is C.** *(Chap. 318)* Impaired lipolysis can lead to steatorrhea and can occur in the presence of pancreatic insufficiency due to chronic pancreatitis in adults or cystic fibrosis in children and adolescents. Normal lipolysis can be maintained by ~5% of maximal pancreatic lipase secretion; thus, steatorrhea is a late manifestation of these disorders. Steatorrhea can also result from impaired movement of fatty acids across the unstirred aqueous fluid layer in two situations: (1) an increase in the relative thickness of the unstirred water layer that occurs in bacterial overgrowth syndromes secondary to functional stasis (e.g., scleroderma) and (2) a decrease in the duodenal concentration of conjugated bile acids below the critical micelle concentration, resulting in impaired micelle formation. Impaired lipid absorption as a result of mucosal inflammation (e.g., celiac disease) and/or intestinal resection can also lead to steatorrhea. Abnormalities of intestinal lymphatics (e.g., intestinal lymphangiectasia) may also be associated with steatorrhea as well as protein loss.

VII-27. **The answer is C.** *(Chap. 319)* Chronic, bloody diarrhea associated with weight loss and systemic symptoms in a young person is highly suggestive of inflammatory bowel disease. The patient's surgical findings suggest discontinuous lesions, which is typical of Crohn disease. Ulcerative colitis, in contrast, typically affects the rectum and proceeds caudally from there without normal mucosa until the area of inflammation terminates. The presence of strictures and fissures further supports the diagnosis of Crohn disease, as these are not features of ulcerative colitis. Microscopically, both ulcerative colitis and Crohn disease may have crypt abscess, and although Crohn disease is more often transmural, full-thickness disease may be present in ulcerative colitis. The hallmark of Crohn disease is granulomas that may be present throughout the bowel wall and involve the lymph nodes, mesentery, peritoneum, liver, and pancreas. Although pathognomonic for Crohn disease, granulomas are only found in about half of surgical resections. Flat villi are not always present in either disease and are more commonly found in isolation with celiac disease.

VII-28. **The answer is D.** *(Chap. 319)* There are a number of dermatologic manifestations of inflammatory bowel disease (IBD), and each type of IBD has a particular predilection for different dermatologic conditions. This patient has pyoderma gangrenosum. Pyoderma gangrenosum can occur in up to 12% of patients with ulcerative colitis and is characterized by a lesion that begins as a pustule and progresses concentrically to surrounding normal skin. The lesions ulcerate with violaceous, heaped margins and surrounding erythema.

They are typically found on the lower extremities. Often the lesions are difficult to treat and respond poorly to colectomy; similarly, pyoderma gangrenosum is not prevented by colectomy. Treatment commonly includes IV antibiotics, glucocorticoids, dapsone, infliximab, and other immunomodulatory agents. Erythema nodosum is more common in Crohn disease and attacks correlate with bowel symptoms. The lesions are typically multiple, red hot, tender nodules measuring 1–5 cm and are found on the lower legs and arms. Psoriasis is more common in ulcerative colitis. Finally, pyoderma vegetans is a rare disorder in intertriginous areas reported to be manifestation of IBD in the skin.

VII-29. **The answer is C.** *(Chap. 319)* There is a protective effect of previous appendectomy with confirmed appendicitis (risk reduction of 13–26%), particularly at a young age, on the development of ulcerative colitis (UC) across different geographical regions and populations. There is an association between antibiotic use and the development of childhood inflammatory bowel disease (IBD) with children who received one or more dispensations of antibiotics during the first year of life having a 2.9-fold increase in the risk of developing IBD during childhood. Peak incidence of UC and Crohn Disease (CD) is in the second to fourth decades, with 78% of CD studies and 51% of UC studies reporting the highest incidence among those aged 20–29 years old. A second modest rise in incidence occurs between the seventh and ninth decades of life. In countries that are becoming more westernized, including China, South Korea, India, Lebanon, Iran, Thailand, and countries in the French West Indies and North Africa, IBD appears to be emerging, emphasizing the importance of environmental factors in disease pathogenesis. The highest incidence rates of CD and UC have been reported in northern Europe, the United Kingdom, and North America.

VII-30. **The answer is C.** *(Chap. 319)* Azathioprine may be used as monotherapy in Crohn disease but is often used in combination with a biologic agent such as an anti–tumor necrosis factor therapy. Cyclosporine A is more commonly used in severe ulcerative colitis but given evidence of equal effectiveness, many providers prefer biologic therapies such as infliximab. Intermittent infusions of infliximab are discouraged since intermittent as opposed to regular (i.e., every 8 week) infusions increases the risk of antibody formation, which can reduce effectiveness and cause infusion-related symptoms. Maintenance prednisone should not be used in the management of Crohn disease given the potential for long-term side effects. Golimumab is approved by the Food and Drug Administration for the treatment of severe ulcerative colitis.

VII-31. **The answer is C.** *(Chap. 320)* Irritable bowel syndrome (IBS) is characterized by recurrence of lower abdominal pain with altered bowel habits over a period of time without progressive deterioration, onset of symptoms during periods of stress or emotional upset, absence of other systemic symptoms such as fever and weight loss, and small-volume stool without evidence of blood. Warning signs that the symptoms may be due to something other than IBS include presentation for the first time in old age, progressive course from the time of onset, persistent diarrhea after a 48-hour fast, and the presence of nocturnal diarrhea or steatorrheal stools. Each patient, except for patient C, has “warning” symptoms that should prompt further evaluation.

VII-32. **The answer is D.** *(Chap. 320)* Up to 80% of patients with irritable bowel syndrome (IBS) also have abnormal psychiatric features; however, no single psychiatric diagnosis predominates. The mechanism is not well understood but may involve altered pain thresholds. Although these patients are hypersensitive to colonic stimuli, this does not carry over to the peripheral nervous system. Functional brain imaging shows disparate activation in, for example, the mid-cingulate cortex, but brain anatomy does not discriminate IBS patients from those without IBS. An association between a history of sexual abuse and IBS has been reported. There is no reported association with sexually transmitted diseases. Patients with IBS do not have an increased risk of autoimmunity.

VII-33. **The answer is C.** *(Chap. 320)* Gut dysbiosis acting in concert with genetic and environmental factors may alter intestinal permeability and increase antigen presentation, resulting in mast cell activation. Products of mast cell degranulation may alter neuronal and smooth muscle function causing irritable bowel syndrome (IBS) symptoms. The cytokines and chemokines generated from mucosal inflammation may cause symptoms such as fibromyalgia, chronic fatigue, and mood changes. IBS may be induced by gastrointestinal infection. About a third of IBS patients experienced an acute "gastroenteritis-like" illness at the onset of their chronic IBS symptomatology. This group of "postinfective" IBS occurs more commonly in females and affects younger rather than older patients. Patients with IBS frequently complain of abdominal distention and increased belching or flatulence, all of which they attribute to increased gas, but most patients who complain of increased gas generate no more than a normal amount of intestinal gas. Most IBS patients have impaired transit and tolerance of intestinal gas loads. As with studies of motor activity, IBS patients frequently exhibit exaggerated sensory responses to visceral stimulation. The frequency of perceptions of food intolerance is at least twofold more common than in the general population. Some (but not most) patients with IBS display persistent signs of low-grade mucosal inflammation with activated lymphocytes, mast cells, and enhanced expression of proinflammatory cytokines. Other studies also indicate that peripheral blood mononuclear cells from IBS patients show abnormal release of proinflammatory cytokines such as interleukin (IL)-6, IL-1β, and tumor necrosis factor. These abnormalities may contribute to abnormal epithelial secretion and visceral hypersensitivity.

VII-34. **The answer is B.** *(Chap. 320)* Physiologic studies demonstrate that anticholinergic drugs inhibit the gastrocolic reflex; hence, postprandial pain is best managed by giving antispasmodics 30 minutes before meals so that effective blood levels are achieved shortly before the anticipated onset of pain. Fiber supplementation with psyllium has been shown to reduce perception of rectal distention, indicating that fiber may have a positive effect on visceral afferent function. This would not, however, be expected to help with postprandial pain. Avoiding flatulogenic foods, exercising, losing excess weight, and taking activated charcoal are safe but unproven remedies for excessive gas, so it is unclear if they would be effective in this case. The selective serotonin reuptake inhibitor (SSRI), citalopram, blunts perception of rectal distention and reduces the magnitude of the gastrocolic response in healthy volunteers. However, SSRIs have not been definitively shown to decrease pain in IBS patients.

VII-35. **The answer is B.** *(Chap. 321)* The patient presents with classic signs of diverticulitis with fever, abdominal pain that is usually left lower quadrant, anorexia or obstipation, and leukocytosis. This most commonly occurs in older individuals. Patients may present with an acute abdomen due to perforation, although this occurs in <25% of cases. Plain radiographs of the abdomen are seldom helpful but may show the presence of an air-fluid level in the left lower quadrant indicating a giant diverticulum with impending perforation. CT with oral contrast is the diagnostic modality of choice with the following findings: sigmoid diverticula, thickened colonic wall >4 mm, and inflammation within the pericolic space with or without the collection of contrast material or fluid. In 16% of patients, an abdominal abscess may be present. Symptoms of IBS may mimic those of diverticulitis. Therefore, suspected diverticulitis that does not meet CT criteria or is not associated with a leukocytosis or fever is not diverticular disease. Other conditions that can mimic diverticular disease include an ovarian cyst, endometriosis, acute appendicitis, and pelvic inflammatory disease. Although the benefit of colonoscopy in the evaluation of patients with diverticular disease has been called into question, its use is still considered important in the exclusion of colorectal cancer. The parallel epidemiology of colorectal cancer and diverticular disease provides enough concern for an endoscopic evaluation before operative management. Therefore, a colonoscopy should be performed approximately 6 weeks after an attack of diverticular disease. Although diverticular disease may result in hematochezia, this finding is generally not temporally linked to diverticulitis.

VII-36. **The answer is B.** *(Chap. 321)* Hemorrhoids can be internal or external; however, they are normally internal and may prolapse to the external position. Hemorrhoids are staged in the following manner: stage I, enlargement with bleeding; stage II, protrusion with spontaneous reduction; stage III, protrusion requiring manual reduction; and stage IV, irreducible protrusion. Stage I, which this patient has, is treated with fiber supplementation, cortisone suppositories, and/or sclerotherapy. Stage II hemorrhoids are treated with fiber and cortisone suppositories. Stage III is offered the prior three therapies and banding or operative hemorrhoidectomy. Patients with stage IV hemorrhoids benefit from fiber and cortisone therapy as well as operative hemorrhoidectomy. Although substantial upper gastrointestinal bleeding may result in hematochezia, the absence of suggestive signs/symptoms and the consistent findings of hemorrhoids do not indicate the need for upper endoscopy in this case.

VII-37. **The answer is C.** *(Chap. 321)* This patient has symptoms (social isolation), signs (foul odor), and risk factors (multiparity) for procidentia (rectal prolapse) and fecal incontinence. Procidentia is far more common in women than men and is often associated with pelvic floor disorders. It is not uncommon for these patients to become socially withdrawn and suffer from depression because of the associated fecal incontinence. The foul odor is a result of poor perianal hygiene due to the prolapsed rectum. Although depression in the elderly is an important medical problem, it is too premature in the evaluation to initiate medical therapy for depression. Occult malignancy and thyroid abnormalities may cause fecal incontinence and depression, but a physical examination would be diagnostic and avoid costly tests. Often patients are concerned they have a rectal mass or carcinoma. Examination after an enema often makes the prolapse apparent. Medical therapy is limited to stool-bulking agents or fiber. Surgical correction is the mainstay of therapy.

VII-38. **The answer is D.** *(Chap. 321)* Patients with diverticular disease may benefit from a fiber-enriched diet that includes 30 g of fiber each day. The use of fiber increases colonic transit time, and, therefore, prevents increased intraluminal pressure leading to the development of diverticulosis. Diverticular disease is considered a functional bowel disorder associated with low-grade inflammation. However, the use of anti-inflammatory medications (mesalazine) in randomized clinical trials have not demonstrated any effect on recurrence rates over placebo alone. Probiotics containing *Lactobacillus acidophilus* and *Bifidobacterium* strains may be beneficial, but they have not been definitively shown to reduce the risk of symptomatic disease. The historical recommendation to avoid eating nuts is based on no more than anecdotal data. Colonoscopy should be considered 6 weeks after resolution of acute diverticulitis to rule out colon cancer. In the absence of complicated diverticular disease there is no indication for surgery following a single bout of diverticulitis. However, patients on immunosuppressive therapy, in chronic renal failure, or with a collagen-vascular disease have a fivefold greater risk of perforation during recurrent attacks. Surgical therapy is indicated in all low-surgical-risk patients with complicated diverticular disease.

VII-39. **The answer is A.** *(Chap. 321)* This patient has a perianal abscess. The development of a perianal abscess is more common in men than women by a ratio of 3:1. The peak incidence is in the third to fifth decade of life and it is more prevalent in immunocompromised patients such as those with diabetes, hematologic disorders, inflammatory bowel disease, and HIV. The other therapies listed are for management of noninfected hemorrhoids. While hemorrhoids can protrude from the anal canal, the presence of fever and a fluctuant mass are atypical for hemorrhoids.

VII-40. **The answer is D.** *(Chap. 322)* This patient with a history of atherosclerotic cardiovascular disease and diabetes is at high risk for nonocclusive mesenteric ischemia in the setting of sepsis, hypotension, and administered vasoconstrictors. Intestinal ischemia is further classified based on etiology, which dictates management (Table VII-40): (1) arterial occlusive mesenteric ischemia, (2) nonocclusive mesenteric ischemia, and (3) mesenteric venous thrombosis. Risk factors for arterial occlusive mesenteric ischemia are generally acute in onset and include atrial fibrillation, recent myocardial infarction, valvular heart disease, and recent cardiac or vascular catheterization, all of which result in embolic clot reaching the mesenteric circulation. Nonocclusive mesenteric ischemia, also known as "intestinal angina," is generally more insidious and most often seen in the aging population affected by atherosclerotic disease. Nonocclusive mesenteric ischemia

TABLE VII-40 Overview of the Management of Acute Intestinal Ischemia

Condition	Key to Early Diagnosis	Treatment of Underlying Cause	Treatment of Specific Lesion	Treatment of Systemic Consequence
Arterio-occlusive mesenteric ischemia 1. Arterial embolus	CT angiography Early laparotomy	Anticoagulation Cardioversion Proximal thrombectomy	Laparotomy Embolectomy Vascular bypass Assess viability and resect dead bowel	Ensure hydration Give antibiotics Reverse acidosis Optimize oxygen delivery Avoid vasoconstrictors
2. Arterial thrombosis	Duplex ultrasound Angiography	Anticoagulation Hydration	Endovascular approach: thrombolysis, angioplasty and stenting Endarterectomy/thrombectomy or vascular bypass Assess viability and resect dead bowel	Give antibiotics Reverse acidosis Optimize oxygen delivery Support cardiac output Avoid vasoconstrictors
Mesenteric venous thrombosis Venous thrombosis	Spiral CT Angiography with venous phase	Anticoagulation Massive hydration	Anticoagulation ± laparotomy/thrombectomy/catheter–directed thrombolysis Assess viability and resect dead bowel	Give antibiotics Reverse acidosis Optimize oxygen delivery Support cardiac output Avoid vasoconstrictors
Nonocclusive mesenteric ischemia	Vasospasm: Angiography Hypoperfusion: Spiral CT or colonoscopy	Ensure hydration Support cardiac output Avoid vasoconstrictors	Vasospasm Intra-arterial vasodilators Hypoperfusion Delayed laparotomy Assess viability and resect dead bowel	Ensure hydration Give antibiotics Reverse acidosis Optimize oxygen delivery Support cardiac output Avoid vasoconstrictors

Source: Modified with permission from Cameron JL: *Current Surgical Therapy*, 2nd ed. Toronto: BC Decker, 1986.

is also seen in patients receiving high-dose vasopressor infusions, patients with cardiogenic or septic shock, and patients with cocaine overdose. Nonocclusive mesenteric ischemia is the most prevalent gastrointestinal disease complicating cardiovascular surgery. Mesenteric venous thrombosis is less common and is associated with the presence of a hypercoagulable state including protein C or S deficiency, anti–thrombin III deficiency, polycythemia vera, and carcinoma. In the absence of atrial fibrillation, nonocclusive mesenteric ischemia is more likely in this patient. There is no reason to suspect inflammatory bowel disease as a cause of the bloody stools in this critically ill patient with known bacteremic sepsis, and the patient has only been on antibiotics for 1 day and is unlikely to have *Clostridium difficile* colitis at this point.

VII-41. **The answer is E.** *(Chap. 322)* Chronic intestinal ischemia presents with intestinal angina or postprandial abdominal pain associated with increased blood flow demand to the intestine following meals. Patients report abdominal cramping and pain following ingestion of a meal. Weight loss and chronic diarrhea may also be noted. Abdominal pain without weight loss is not chronic mesenteric angina. The gold standard for confirmation of mesenteric arterial occlusion is mesenteric angiography. Evaluation with mesenteric angiography allows for identification and possible intervention for the treatment of atherosclerosis within the vessel lumen and will also evaluate the patency of remaining mesenteric vessels. A noncontrast CT might show calcifications in mesenteric vessels but would not show the patency of those vessels. Atrial fibrillation increases the risk for acute mesenteric ischemia from thromboembolism but its presence or absence would not aid in the diagnosis of chronic ischemia. A high-fiber diet would potentially help if this patient's symptoms were from irritable bowel syndrome, but her age, known atherosclerotic disease, and weight loss would make that a less likely diagnosis. Although depression can lead to chronic pain and weight loss, the more life-threatening diagnosis of chronic intestinal ischemia needs to be considered first.

VII-42. **The answer is B.** *(Chap. 323)* The radiograph shows a massively dilated colon extending to the rectum. This radiograph is consistent with colonic pseudo-obstruction or Ogilvie syndrome. Ogilvie syndrome may be seen in elderly patients after nonabdominal surgery or in patients with underlying autonomic dysfunction. The presence of gas in the colon makes small bowel obstruction unlikely. There is no extraintestinal air that would be suggestive of small or large bowel perforation. Small bowel ileus is characterized by multiple small bowel air-fluid levels on radiograph. The differential for extensive colonic dilation includes toxic megacolon due to *Clostridium difficile* infection. In this case, that is less likely given the recent surgery and lack of antibiotic treatment.

VII-43. The answer is D. *(Chap. 323)* This patient likely has a small bowel obstruction as evidenced by his symptoms, examination findings, and presence of air-fluid levels and dilated small bowel loops on the CT scan. While the most common cause of small bowel obstruction is postsurgical adhesions, a number of other conditions can lead to acute small bowel obstruction (Table VII-43). While he does have a history atrial fibrillation in the past, the presentation is not consistent with acute mesenteric ischemia and he is currently in sinus rhythm. He has no clear signs or symptoms of acute cholecystitis and the normal right upper quadrant ultrasound is reassuring that he does not have gallstone pancreatitis with a resulting ileus.

TABLE VII-43 Acute Small-Intestinal and Colonic Obstruction Incidences

Cause	Incidence
Postoperative adhesions	>50%
Neoplasms	~20%
Hernias (especially ventral or internal types, where the risk of strangulation is increased)	~10%
Inflammatory bowel disease, other inflammation (obstruction may resolve if acute inflammation and edema subside)	~5%
Intussusception, volvulus, other miscellaneous diseases	<15%

VII-44. The answer is A. *(Chap. 324)* The patient presents with typical findings for acute appendicitis with anorexia, progressing to vague periumbilical pain, followed by localization to the right lower quadrant. Low-grade fever and leukocytosis are frequently present. Although acute appendicitis is primarily a clinical diagnosis, imaging modalities are frequently employed because the symptoms are not always classic. Plain radiographs are rarely helpful except when an opaque fecalith is found in the right lower quadrant (<5% of cases). Ultrasound may demonstrate an enlarged appendix with a thick wall but is most useful to rule out ovarian pathology, tubo-ovarian abscess, or ectopic pregnancy. The effectiveness of ultrasonography as a tool to diagnose appendicitis is highly operator dependent. Even in very skilled hands, the appendix may not be visualized. Its overall sensitivity is 0.86, with a specificity of 0.81. Nonenhanced and contrast-enhanced CT are superior to ultrasound or plain radiograph in the diagnosis of acute appendicitis with a sensitivity of 0.94 and specificity of 0.95. Findings often include a thickened appendix with periappendiceal stranding and often the presence of a fecalith (Figure VII-44). Free air is uncommon, even in the case of a perforated appendix. Nonvisualization of the

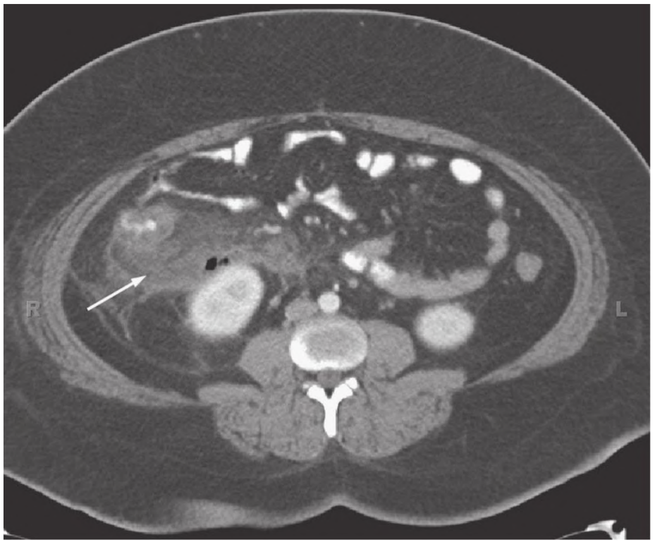


FIGURE VII-44

appendix on CT is associated with surgical findings of a normal appendix 98% of the time. Colonoscopy has no role in the diagnosis of acute appendicitis.

VII-45. The answer is E. *(Chap. 324)* This patient likely has acute appendicitis. Laparoscopic appendectomy is preferred over an open procedure because of less postoperative pain, shorter lengths of stay, faster return to normal activity, and likely fewer superficial wound complications. There may be a higher risk of intra-abdominal abscess formation with the laparoscopic approach. Although some bouts of appendicitis might resolve on their own or with antibiotic therapy, it is difficult to predict which patients will develop a perforation or abscess, so surgical therapy is most commonly offered in a patient with no contraindications to surgical therapy. IV corticosteroids would not be helpful and might increase the risk of infection. Colonoscopy has no role in the management of acute appendicitis.

VII-46. The answer is C. *(Chap. 324)* The patient presents with several months of epigastric abdominal pain that is worse after eating. His symptoms are highly suggestive of peptic ulcer disease, with the worsening pain after eating suggesting a duodenal ulcer. The current presentation with an acute abdomen and free air under the diaphragm points to a diagnosis of perforated viscus. Perforated gallbladder is less likely in light of the duration of symptoms and the absence of the significant systemic symptoms that often accompany this condition. Because the patient is relatively young with no risk factors for mesenteric ischemia, necrotic bowel from an infarction is highly unlikely. Pancreatitis can have a similar presentation, but the pancreas cannot perforate and liberate free air. This patient likely has peritonitis caused by the presence of gastric contents in the peritoneal space.

VII-47. The answer is C. *(Chap. 324)* Arriving at the diagnosis of appendicitis can be challenging when the appendix is not located in the right lower quadrant, in women of childbearing age, and in the very young or elderly. Patients with pelvic appendicitis commonly present with dysuria, urinary frequency, diarrhea, or tenesmus. For this reason a pelvic and rectal examination should be performed in patients with suspected appendicitis. Anorexia is such a common symptom in appendicitis that its absence should prompt a search for an alternative diagnosis. Classically, maximal tenderness is identified in the right lower quadrant at or near McBurney point, which is located approximately one-third of the way along a line originating at the anterior iliac spine and running to the umbilicus. Right lower quadrant tenderness is present in over 90% of patients with appendicitis, while Rovsing sign, which is pain in the right lower quadrant during left lower quadrant palpation, is only present in 5% of patients with acute appendicitis (Table VII-47).

TABLE VII-47 Relative Frequency of Some Presenting Signs

Signs	Frequency (%)
Abdominal tenderness	>95
Right lower quadrant tenderness	>90
Rebound tenderness	30–70
Rectal tenderness	30–40
Cervical motion tenderness	30
Rigidity	~10
Psoas sign	3–5
Obturator sign	5–10
Rovsing sign	5
Palpable mass	<5

VII-48. The answer is B. *(Chap. 325)* Carbohydrates, proteins, and fats are the primary sources of nutrients in the diet. The largest source of calories and nutrients in the diet is carbohydrates. At least 45–55% of a person's total calories are derived from carbohydrates. The second biggest source of calories in the diet is fats. Although it is recommended that no more than 30% of one's calories come from fats, a typical American diet consists of about 34% fat. Proteins contribute 10–15% of daily caloric intake. Finally, although alcohol can contribute calories to one's diet, it does not contribute any nutrients.

VII-49. **The answer is A.** *(Chap. 325)* Evaporation and exhalation can account for 500–1000 mL of water loss per day. Normal stool output includes about 50–100 mL of water per day. Pregnancy increases daily water needs by about 30 mL/d. Urine output would be expected to be lower in a person with a lower solute load. Fever can increase water needs by up to 200 mL/d.

VII-50. **The answer is D.** *(Chap. 326)* This patient is manifesting symptoms of thiamine deficiency. The most common causes of thiamine deficiency in developed countries are alcoholism and chronic illnesses such as cancer. Alcohol interferes with the absorption of thiamine as well as the synthesis of thiamine pyrophosphate. In addition, alcohol increases the excretion of thiamine in the urine. Moreover, most chronic alcoholics have low dietary intake of thiamine. Chronic thiamine deficiency manifests as beriberi, which is classically described as "wet" or "dry," depending on whether significant heart failure symptoms are present. However, there is often overlap between the syndromes of "wet" and "dry" beriberi. Both forms of the disease often exhibit paresthesias and neuropathic pain. Wet beriberi symptoms include those of high-output heart failure with tachycardia, cardiomegaly, and peripheral edema. Dry beriberi symptoms more commonly are those of both a motor and sensory neuropathy, predominantly affecting the legs. Alcoholic patients also demonstrate central nervous system effects. Acutely, this can consist of horizontal nystagmus, ophthalmoplegia, cerebellar ataxia, and mental impairment. This constellation of findings is called Wernicke encephalopathy. When there is additional loss of memory with confabulatory psychosis, as this individual is exhibiting, the syndrome is called Wernicke-Korsakoff syndrome. Rehydration with glucose-containing solutions without thiamine repletion can precipitate acute worsening of thiamine deficiency with lactic acidosis and coma and should be studiously avoided. In this case, the IV fluids with glucose should be held until thiamine repletion has begun. Thiamine should be repleted at a dose of 200 mg IV three times daily until there is no further improvement in acute symptoms, and then long-term oral thiamine at a dose of 10 mg daily should be continued until recovery is complete. In cases of Wernicke-Korsakoff syndrome, long-term memory loss is common.

VII-51. **The answer is B.** *(Chap. 326)* Niacin (vitamin B_3) has high bioavailability from beans, milk, meat, and eggs. While the bioavailability from grains is lower, most flour is enriched with "free" niacin; thus, deficiency of niacin is rare in western diets. Niacin deficiency can be found in individuals with corn-based diets in some parts of China, Africa, and India; individuals with alcoholism; and individuals with genetic defects limiting absorption of tryptophan. In addition, individuals with carcinoid syndrome are at increased risk of niacin deficiency because of increased conversion of tryptophan to serotonin. Clinically, the syndrome of niacin deficiency is known as pellagra. Early symptoms of niacin deficiency are loss of appetite, generalized weakness, abdominal pain, and vomiting. Glossitis is characteristic of pellagra with a beefy red tongue. Pellagra also has many dermatologic manifestations including a characteristic skin rash appearing on sun-exposed areas. The rash is typically scaling and erythematous. Often, the rash forms a ring around the neck, known as the Casal necklace. The four d's of niacin deficiency—diarrhea, dermatitis, dementia, and death—are seen only in the most severe cases.

VII-52. **The answer is D.** *(Chap. 326)* This patient presents with gingival bleeding and has the classic perifollicular hemorrhagic rash of scurvy (vitamin C deficiency). In the United States, scurvy is primarily a disease of alcoholics and the elderly who consume <10 mg/d of vitamin C. Other individuals who are at risk of the disease are the poor and those who consume macrobiotic diets that are high in grains and seafood but avoid citrus fruits. In addition to nonspecific symptoms of fatigue, these patients also have impaired ability to form mature connective tissue and can bleed into various sites, including the joints, skin, and gingiva. A normal international normalized ratio excludes symptomatic vitamin K deficiency. Thiamine, niacin, and folate deficiencies are also seen in patients with alcoholism. Thiamine deficiency may cause peripheral neuropathy (beriberi), high-output heart failure, ataxia, and memory impairment. Folate deficiency causes macrocytic anemia and thrombocytopenia. Niacin deficiency causes pellagra, which is characterized by glossitis and a pigmented, scaling rash that may be particularly noticeable in sun-exposed areas.

VII-53. **The answer is D.** *(Chap. 326)* This patient likely developed vitamin B_6 deficiency as a result of isoniazid treatment in the absence of taking pyridoxine. Vitamin B_6 refers to a family of compounds that includes pyridoxine, pyridoxal, pyridoxamine, and their 5′-phosphate derivatives. 5′-Pyridoxal phosphate (PLP) is a cofactor for >100 enzymes involved in amino acid metabolism. Vitamin B_6 also is involved in heme and neurotransmitter synthesis and in the metabolism of glycogen, lipids, steroids, sphingoid bases, and several vitamins, including the conversion of tryptophan to niacin. Certain medications, such as isoniazid, L-dopa, penicillamine, and cycloserine, interact with PLP due to a reaction with carbonyl groups. In the case of isoniazid, this results in a functional deficiency of pyridoxine that can lead to peripheral neuropathy. Pyridoxine should be given to all patients who are taking isoniazid to avoid this complication.

VII-54. **The answer is C.** *(Chap. 326)* This child likely has vitamin A deficiency. Vitamin A deficiency worldwide is present in 190 million preschool-age children, among whom >5 million have an ocular manifestation of deficiency termed xerophthalmia. This condition includes milder stages of night blindness and conjunctival xerosis (dryness) with Bitot spots (white patches of keratinized epithelium appearing on the sclera) that may affect 1–5% of children in deficient populations as well as rare, potentially blinding corneal ulceration and necrosis. Keratomalacia (softening of the cornea) leads to corneal scarring that blinds an estimated quarter of a million children each year and is associated with fatality rates of 4–25%. Vitamin A deficiency can compromise barrier, innate, and acquired immune defenses to infection. Supplementation in areas of endemic deficiency can markedly reduce mortality. Maternal vitamin A deficiency is a common cause of night blindness and can also increase the risk of maternal death from infection.

VII-55. **The answer is E.** *(Chap. 327)* The patient in this scenario has evidence of chronic starvation-related malnutrition, most likely related to anorexia nervosa. Starvation-related malnutrition that occurs without evidence of systemic inflammation is also known as marasmus and develops over months or years due to prolonged decreases in energy and protein intake. The patient exhibits a starved appearance with a low body mass index (<18.5 kg/m^2). The diagnosis is based on diminished skinfold thickness, which reflects loss of fat stores and reduced arm circumference and demonstrates muscle wasting. In addition, temporal and interosseous muscle wasting is also commonly seen. Routine laboratory testing is not remarkably abnormal. Albumin may be low, but it is typically not less than 2.8 g/dL. However, despite a morbid appearance, immunocompetence and wound healing are preserved. Because the process is a chronic and fairly well-adapted process, treatment should be planned in concert with a dietitian to slowly allow a return to normal body weight. Overly aggressive nutritional support can lead to life-threatening metabolic imbalances. When mortality occurs in anorexia nervosa, it is most commonly related to complications of the disease and rarely due to malnutrition itself. Indeed, suicide is a more common cause of death in the disease than malnutrition. In certain processes such as cancer or chronic obstructive pulmonary disease, a similar loss of fat and protein can occur in the setting of systemic inflammation resulting in a wasted appearance. This process is known as cachexia. The diagnostic criteria are similar with regard to skinfold thickness and arm circumference. However, due to the concomitant systemic inflammation, individuals with cachexia are more likely to have lower albumin levels and can be immunocompromised.

VII-56. **The answer is B.** *(Chap. 327)* A patient's basal energy expenditure (BEE) can be calculated by the Harris-Benedict equation. The factors that are used for determining BEE are age, gender, height, and weight. The BEE for hospitalized patients is then adjusted by a factor of 1.1–1.4 depending on the severity of illness, with the highest values used for patients admitted with marked stress such as trauma or severe sepsis. The BEE serves as an estimate only. If it is important to have an exact calculation of energy expenditure, indirect calorimetry can be performed. Protein needs can also be calculated more definitively by the use of urine urea nitrogen as an estimate of protein catabolism.

VII-57. **The answer is B.** *(Chap. 327)* Starvation-associated malnutrition is chronic starvation without inflammation (anorexia nervosa or major depression with lack of interest in eating). Chronic disease-associated malnutrition occurs when inflammation is chronic and of mild to moderate degree (e.g., organ failure, pancreatic cancer, or sarcopenic obesity). Acute disease or injury-associated malnutrition occurs when inflammation is acute and of severe degree (e.g., major infection, burns, trauma, or closed head injury).

VII-58. **The answer is E.** *(Chap. 327)* Dual energy x-ray absorptiometry (DEXA) is often used to measure bone density but it can also be for soft tissue measurements with appropriate software. DEXA can compare truncal and appendicular soft tissue components but does have the disadvantage of a modest x-ray exposure. Anthropomorphic analyses such as measuring skinfolds and circumferences require training for reliability. The typical coefficient of variation is ≥10%. Bioelectrical impedance is based on differential resistance of body tissues. The equipment is easily portable and provides good measurement of body water. This method requires population specific validation of regression equations. Albumin, with a serum half-life of 14–20 days, lacks sensitivity and specificity for malnutrition. It is a potent risk indicator for morbidity and mortality. It is a proxy measure for underlying injury, disease, or inflammation. In addition to malnutrition, a low albumin can be caused by liver disease, nephrotic syndrome, and protein-wasting enteropathy. C-reactive protein is a positive acute phase reactant. It is generally elevated if an active inflammatory process is manifest but it is not specific for malnutrition.

VII-59. **The answer is A.** *(Chap. 329)* The most common and most characteristic symptom of liver disease is fatigue. Unfortunately, it is also very nonspecific, with little specific diagnostic utility. The fatigue in liver disease seems to improve in the morning and worsen throughout the day, but it can be intermittent. Jaundice is the hallmark of liver disease and is much more specific. Jaundice, however, is typically a sign of more advanced disease. Itching is also typically a symptom of more advanced disease and is more common in cholestatic causes of liver disease. Nausea often occurs in severe disease and can be accompanied by vomiting. Right upper quadrant pain is a less common symptom and indicates stretching of the liver capsule.

VII-60. **The answer is A.** *(Chap. 329)* In assessing alcohol intake, the history should also focus on whether alcohol abuse or dependence is present. Alcoholism is usually defined by the behavioral patterns and consequences of alcohol intake, not by the amount. Abuse is defined by a repetitive pattern of drinking alcohol that has adverse effects on social, family, occupational, or health status. Dependence is defined by alcohol-seeking behavior, despite its adverse effects. Many alcoholics demonstrate both dependence and abuse, and dependence is considered the more serious and advanced form of alcoholism. A clinically helpful approach to diagnosis of alcohol dependence and abuse is the use of the CAGE questionnaire, which is recommended for all medical history taking. One "yes" response should raise suspicion of an alcohol use problem, and more than one "yes" response is a strong indication of abuse of dependence.

VII-61. **The answer is C.** *(Chap. 329)* While there are many causes of liver disease, these disorders generally present clinically in a few distinct patterns and are usually classified as hepatocellular, cholestatic (obstructive), or mixed (Table VII-61). In hepatocellular diseases (such as viral hepatitis and alcoholic liver disease), features of liver injury, inflammation, and necrosis predominate. In cholestatic diseases, such as gallstones or malignant obstruction, primary biliary cholangitis (previously referred to as primary biliary cirrhosis), and some drug-induced liver diseases, features of inhibition of bile flow predominate. In a mixed pattern, features of both hepatocellular and cholestatic injury are present (such as in cholestatic forms of viral hepatitis and many drug-induced liver diseases).

TABLE VII-61 Liver Diseases

Inherited hyperbilirubinemia
- Gilbert syndrome
- Crigler-Najjar syndrome, types 1 and 2
- Dubin-Johnson syndrome
- Rotor syndrome

Viral hepatitis
- Hepatitis A
- Hepatitis B
- Hepatitis C
- Hepatitis D
- Hepatitis E
- Others (Epstein-Barr virus [mononucleosis] herpesvirus, cytomegalovirus, adenovirus hepatitis)
- Cryptogenic hepatitis

Immune and autoimmune liver diseases
- Primary biliary cholangitis
- Autoimmune hepatitis
- Sclerosing cholangitis
- Overlap syndromes
- Graft-versus-host disease
- Allograft rejection

Genetic liver diseases
- Alpha-1 antitrypsin deficiency
- Hemochromatosis
- Wilson disease
- Benign recurrent intrahepatic cholestasis
- Progressive familial intrahepatic cholestasis, types I–III
- Others (galactosemia, tyrosinemia, cystic fibrosis, Niemann-Pick-disease, Gaucher disease)

Alcoholic liver disease
- Acute fatty liver
- Acute alcoholic hepatitis
- Laënnec cirrhosis

Nonalcoholic fatty liver
- Steatosis
- Steatohepatitis

Acute fatty liver of pregnancy

Liver involvement in systemic diseases
- Sarcoidosis
- Amyloidosis
- Glycogen storage diseases
- Celiac disease
- Tuberculosis
- *Mycobacterium avium-intracellulare* infection

Cholestatic syndromes
- Benign postoperative cholestasis
- Jaundice of sepsis
- Total parenteral-nutrition–induced jaundice
- Cholestasis of pregnancy
- Cholangitis and cholecystitis
- Extrahepatic biliary obstruction (stone, stricture, cancer)
- Biliary atresia
- Caroli disease
- Cryptosporidiosis

Drug-induced liver disease
- Hepatocellular patterns (isoniazid, acetaminophen)
- Cholestatic patterns (methyltestosterone)
- Mixed patterns (sulfonamides, phenytoin)
- Micro- and macrovesicular steatosis (methotrexate, fialuridine)

Vascular injury
- Sinusoidal obstruction syndrome
- Budd-Chiari syndrome
- Ischemic hepatitis
- Passive congestion
- Portal vein thrombosis
- Nodular regenerative hyperplasia

Mass lesions
- Hepatocellular carcinoma
- Cholangiocarcinoma
- Adenoma
- Focal nodular hyperplasia
- Metastatic tumors
- Abscess
- Cysts
- Hemangioma

VII-62. **The answer is B.** *(Chap. 329)* Magnetic resonance cholangiopancreatography (MRCP) and endoscopic retrograde cholangiopancreatography (ERCP) are the procedures of choice for visualization of the biliary tree. MRCP offers several advantages over ERCP: there is no need for contrast media or ionizing radiation, images can be acquired faster, the procedure is less operator dependent, and it carries no risk of pancreatitis. MRCP is superior to ultrasound and CT for detecting choledocholithiasis but is less specific. MRCP is useful in the diagnosis of bile duct obstruction and congenital biliary abnormalities, but ERCP is more valuable in evaluating ampullary lesions and primary sclerosing cholangitis. ERCP permits biopsy, direct visualization of the ampulla and common bile duct, and intraductal ultrasonography and brushings for cytological evaluation of malignancy. It also provides several therapeutic options in patients with obstructive jaundice, such as sphincterotomy, stone extraction, and placement of nasobiliary catheters and biliary stents.

VII-63. **The answer is D.** *(Chap. 330)* It is important to understand the patterns of laboratory abnormalities that indicate liver disease is present. One way to consider laboratory evaluation of liver disease is to consider three general categories of tests: those based on excretory function of the liver, those of biosynthetic activity of the liver, and those of coagulation factors. The most common tests of liver function fall under the category of tests based on the detoxification and excretory function of the liver. These include serum bilirubin, ammonia and enzyme levels, and urine bilirubin. Bilirubin can exist as a conjugated and an unconjugated form. The unconjugated form is often referred to as the indirect portion. Isolated elevation in the unconjugated form of bilirubin is typically not related to liver disease but is most commonly seen in hemolysis and a number of benign genetic conditions such as Gilbert syndrome. In contrast, conjugated (or direct) hyperbilirubinemia almost always indicates disease of the liver or biliary tract. Conjugated bilirubin is water soluble and excreted in the urine, but unconjugated bilirubin is not; rather, it binds to albumin in the blood. Therefore, bilirubinuria implies liver disease as well. Among the serum enzymes, it is useful to consider enzymes as those that are associated with hepatocellular injury versus those that reflect cholestasis. Alanine and aspartate aminotransferases are the primary enzymes that indicate hepatocyte injury. Alkaline phosphatase is the most common enzyme elevated in cholestasis, but bone disease also causes increased alkaline phosphatase. In some cases, one needs additional information to determine whether the alkaline phosphatase is liver or bone in origin. Other tests that would be elevated in cholestatic liver disease are 5′-nucleotidase and γ-glutamyl transferase. The primary test of hepatic synthetic function is measurement of serum albumin. Coagulation factors can be directly measured, but impaired production of coagulation factors in liver disease is primarily inferred from elevations in prothrombin time.

VII-64. **The answer is B.** *(Chap. 330)* The aminotransferases are sensitive indicators of liver cell injury and are most helpful in recognizing acute hepatocellular diseases such as hepatitis. They include aspartate aminotransferase (AST) and alanine aminotransferase (ALT). AST is found in the liver, cardiac muscle, skeletal muscle, kidneys, brain, pancreas, lungs, leukocytes, and erythrocytes in decreasing order of concentration. ALT is found primarily in the liver and is therefore a more specific indicator of liver injury. The aminotransferases are normally present in the serum in low concentrations. These enzymes are released into the blood in greater amounts when there is damage to the liver cell membrane, resulting in increased permeability. Liver cell necrosis is not required for the release of the aminotransferases, and there is a poor correlation between the degree of liver cell damage and the level of the aminotransferases. Thus, the absolute elevation of the aminotransferases is of no prognostic significance in acute hepatocellular disorders. Any type of liver cell injury can cause modest elevations in the serum aminotransferases. Levels of up to 300 IU/L are nonspecific and may be found in any type of liver disorder. Minimal ALT elevations in asymptomatic blood donors rarely indicate severe liver disease; studies have shown that fatty liver disease is the most likely explanation. Striking elevations—i.e., aminotransferases >1000 IU/L—occur almost exclusively in disorders associated with extensive hepatocellular injury such as viral hepatitis, ischemic liver injury (prolonged hypotension or acute heart failure), or toxin- or drug-induced liver injury. The pattern of the aminotransferase elevation can be helpful diagnostically. In most acute hepatocellular disorders, the ALT is higher than or equal to the AST. Whereas the AST:ALT ratio is typically <1 in patients with chronic viral hepatitis and nonalcoholic fatty liver disease, a number of groups have noted that as cirrhosis develops, this ratio rises to >1. An AST:ALT ratio >2:1 is suggestive, whereas a ratio >3:1 is highly suggestive, of alcoholic liver disease. The AST in alcoholic liver disease is rarely >300 IU/L, and the ALT is often normal. The aminotransferases are usually not greatly elevated in obstructive jaundice.

VII-65. **The answer is B.** *(Chap. 330)* The pattern of the aminotransferase elevation can be helpful diagnostically. In most acute hepatocellular disorders, the alanine aminotransferase (ALT) is higher than or equal to the aspartate aminotransferase (AST). Whereas the AST:ALT ratio is typically <1 in patients with chronic viral hepatitis and nonalcoholic fatty liver disease, a number of groups have noted that as cirrhosis develops, this ratio rises to >1. An AST:ALT ratio >2:1 is suggestive, whereas a ratio >3:1 is highly suggestive, of alcoholic liver disease. The AST in alcoholic liver disease is rarely >300 IU/L, and the ALT is often normal. A low level of ALT in the serum is due to an alcohol-induced deficiency of pyridoxal phosphate. The aminotransferases are usually not greatly elevated in obstructive jaundice. One notable exception occurs during the acute phase of biliary obstruction caused by the passage of a gallstone into the common bile duct. In this setting, the aminotransferases can briefly be in the 1000–2000 IU/L range. However, aminotransferase levels decrease quickly, and the biochemical tests rapidly evolve into those typical of cholestasis.

VII-66. **The answer is D.** *(Chap. 330)* Elevation of liver-derived alkaline phosphatase is not totally specific for cholestasis, and a less than threefold elevation can be seen in almost any type of liver disease. Patients over age 60 can have a mildly elevated alkaline phosphatase (1–1.5 times normal), whereas individuals with blood types O and B can have an elevation of the serum alkaline phosphatase after eating a fatty meal due to the influx of intestinal alkaline phosphatase into the blood. It is also elevated in children and adolescents undergoing rapid bone growth because of bone alkaline phosphatase, and late in normal pregnancies due to the influx of placental alkaline phosphatase. γ-Glutamyl transpeptidase is located in the endoplasmic reticulum and in bile duct epithelial cells and is less specific for cholestasis than are elevations of alkaline phosphatase or 5′-nucleotidase. Diffuse polyclonal increases in IgG levels are common in autoimmune hepatitis; increases >100% should alert the clinician to this possibility. Increases in the IgM levels are common in primary biliary cirrhosis, whereas increases in the IgA levels occur in alcoholic liver disease. With the exception of factor VIII, which is produced by vascular endothelial cells, the blood clotting factors are made exclusively in hepatocytes. Serum albumin has a long half-life: 18–20 days, with ~4% degraded per day. Because of this slow turnover, the serum albumin is not a good indicator of acute or mild hepatic dysfunction.

VII-67. **The answer is E.** *(Chap. 331)* This patient is presenting with an asymptomatic and mild elevation in unconjugated hyperbilirubinemia that has occurred during a time of increased stress, fatigue, and likely decreased caloric intake. This presentation is characteristic of Gilbert syndrome, an inherited disorder of bilirubin conjugation. In Gilbert syndrome, there is a mutation of the *UGT1A1* gene that encodes bilirubin UDP-glucuronosyltransferase, which leads to a reduction in activity on the enzyme to 10 to 35% of normal. This enzyme is of critical importance in the conjugation of bilirubin. Most of the time, there is no apparent jaundice because the reduced ability to conjugate bilirubin is not reduced to a degree that leads to an elevation of bilirubin. However, during times of stress, fatigue, alcohol use, decreased caloric intake, or intercurrent illness, the enzyme can become overwhelmed, leading to a mild hyperbilirubinemia. Typical bilirubin levels are less than 4.0 mg/dL unless the individual is ill or fasting. The level of hyperbilirubinemia may be enough to cause scleral icterus and jaundice. Diagnosis usually occurs during young adulthood, and episodes are self-limited and benign. If a liver biopsy were to be performed (not indicated in this case), hepatic histology would be normal. No treatment is necessary because there are no long-term consequences of Gilbert syndrome, and patient reassurance is recommended. Other inherited disorders of bilirubin conjugation are Crigler-Najjar syndromes types 1 and 2. Crigler-Najjar syndrome type 1 is a congenital disease characterized by more dramatic elevations in bilirubin as high as 20–45 mg/dL that is first diagnosed in the neonatal period and is present throughout life. This rare disorder was once fatal in early childhood due to the development of kernicterus. However, with phototherapy, individuals are now able to survive into adulthood, although neurologic deficits are common. Crigler-Najjar syndrome type 2 is similar to type 1, but the elevations in bilirubin are not as great. Kernicterus is rare. This is because there is some residual function of the bilirubin UDP-glucuronosyltransferase enzyme (<10%), which is totally absent in type 1 disease. Hemolysis is another frequent cause of elevated unconjugated bilirubin. Hemolysis can be caused by many factors including medications, autoimmune disorders, and inherited disorders, among others. However, the normal hematocrit, lactate dehydrogenase, and haptoglobin eliminate hemolysis as a possibility in this case. Dubin-Johnson syndrome is another congenital hyperbilirubinemia. However, it is a predominantly conjugated hyperbilirubinemia caused by a defect in biliary excretion from hepatocytes. Obstructive choledocholithiasis is characterized by right upper quadrant pain that is often exacerbated by fatty meals. The absence of symptoms or elevation in other liver function tests, especially alkaline phosphatase, also makes this diagnosis unlikely.

VII-68. **The answer is B.** *(Chap. 331)* Increased destruction of erythrocytes leads to increased bilirubin turnover and unconjugated hyperbilirubinemia; the hyperbilirubinemia is usually modest in the presence of normal liver function. Hemolysis alone cannot result in a sustained hyperbilirubinemia of more than 4 mg/dL (~68 μmol). Higher values imply concomitant hepatic dysfunction. When hemolysis is the only abnormality in an otherwise healthy individual, the result is a purely unconjugated hyperbilirubinemia, with the direct-reacting fraction as measured in a typical clinical laboratory being ≤15% of the total serum bilirubin. In the presence of systemic disease, which may include a degree of hepatic dysfunction, hemolysis may produce a component of conjugated hyperbilirubinemia in addition to an elevated unconjugated bilirubin concentration. Prolonged hemolysis may lead to the precipitation of bilirubin salts within the gallbladder or biliary tree, resulting in the formation of gallstones in which bilirubin, rather than cholesterol, is the major component. Such pigment stones may lead to acute or chronic cholecystitis, biliary obstruction, or any other biliary tract consequence of calculous disease.

VII-69. **The answer is D.** *(Chap. 331)* This patient likely has Dubin-Johnson Syndrome (DJS). This benign, relatively rare disorder is characterized by low-grade, predominantly conjugated hyperbilirubinemia (Table VII-69). Total bilirubin concentrations are typically between 34 and 85 μmol/L (2 and 5 mg/dL) but on occasion can be in the normal range or as high as 340–430 μmol/L (20–25 mg/dL) and can fluctuate widely in any given patient. The degree of hyperbilirubinemia may be increased by intercurrent illness, oral contraceptive use, and pregnancy. Because the hyperbilirubinemia is due to a predominant rise in conjugated bilirubin, bilirubinuria is characteristically present. Aside from elevated serum bilirubin levels, other routine laboratory tests are normal. Physical examination is usually normal except for jaundice, although an occasional patient may have hepatosplenomegaly. Patients with DJS are usually asymptomatic, although some may have vague constitutional symptoms. In women, the condition may be subclinical until the patient becomes pregnant or receives oral contraceptives, at which time chemical hyperbilirubinemia becomes frank jaundice. Even in these situations, other routine liver function tests, including serum alkaline phosphatase and transaminase activities, are normal. Benign recurrent intrahepatic cholestasis would be expected to have biochemical abnormalities other than isolated hyperbilirubinemia and is often accompanied by intense pruritus. Cholestasis of pregnancy usually occurs in the late second trimester or early third trimester and is most often accompanied by severe pruritus that precedes biochemical abnormalities by several weeks. Crigler-Najjar syndrome type 2 is characterized by marked unconjugated hyperbilirubinemia. HELLP syndrome is characterized

TABLE VII-69 Principal Differential Characteristics of Inheritable Disorders of Bile Canalicular Function

	DJS	Rotor	PFIC1	BRIC1	PFIC2	BRIC2	PFIC3
Gene	*ABCCA*	*SLCO1B1/ SLCO1B3*	*ATP8B1*	*ATP8B1*	*ABCB11*	*ABCB11*	*ABCB4*
Protein	MRP2	OATP1B1/1B3	FIC1	FIC1	BSEP	BSEP	MDR3
Cholestasis	No	No	Yes	Episodic	Yes	Episodic	Yes
Serum GGT	Normal	Normal	Normal	Normal	Normal	Normal	↑↑
Serum bile acids	Normal	Normal	↑↑	↑↑ during episodes	↑↑	↑↑during episodes	↑↑
Clinical features	Mild conjugated hyperbilirubinemia; otherwise normal liver function; dark pigment in liver; characteristic pattern of urinary coproporphyrins	Mild conjugated hyperbilirubinemia; otherwise normal liver function; liver without abnormal pigmentation	Severe cholestasis beginning in childhood	Recurrent episodes of cholestasis beginning at any age	Severe cholestasis beginning in childhood	Recurrent episodes of cholestasis beginning at any age	Severe cholestasis beginning in childhood; decreased phospholipids in bile

Abbreviations: BRIC, benign recurrent intrahepatic cholestasis; BSEP, bile salt excretory protein; DJS, Dubin-Johnson syndrome; GGT, γ-glutamyltransferase; MRP2, multidrug resistance–associated protein 2; OATP1A/1B, organic anion transport proteins 1B1 and 1B3; PFIC, progressive familial intrahepatic cholestasis; ↑↑, increased.

by hemolysis, elevated liver enzymes, and low platelets, and would be expected to have an unconjugated hyperbilirubinemia.

VII-70. **The answer is B.** *(Chap. 332)* This patient presents with acute hepatitis, which has numerous etiologies. These include viruses, toxins/drugs, autoimmune diseases, metabolic diseases, alcohol, ischemia, pregnancy, and other infectious etiologies including rickettsial diseases and leptospirosis. In this clinical scenario, the patient does have risk factors for hepatitis A, B, and C infection, including being a man who has sex with men and a prior history of injection drug use. All acute viral hepatitis presents with a similar clinical pattern, although incubation periods vary after exposure. The most common initial symptoms are fatigue, anorexia, nausea, vomiting, myalgias, and headache. These symptoms precede the onset of jaundice by about 1–2 weeks. Once jaundice develops, the prodromal symptoms regress. On physical examination, there is usually obvious icterus with an enlarged and tender liver. Splenomegaly can occur. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are elevated with peak levels that are quite variable between 400 and 4000 IU/L, and alkaline phosphatase levels are increased to a much lesser degree. Hyperbilirubinemia (levels 5–20 mg/dL) occurs with primarily increased levels of conjugated bilirubin. Thus, it is important to recognize the patterns of antibody production in the viral hepatitides. Hepatitis A is an RNA virus that presents with acute hepatitis and is transmitted by the fecal-oral route. In the acute state, the IgM would be elevated, which is not seen in this scenario. Hepatitis B virus is a DNA virus with three common antigens that are tested serologically to determine the time course of the illness. These antigens are the surface antigen, the core antigen, and the e antigen, which is a nucleocapsid protein produced from the same gene as the core antigen but immunologically distinct. Several distinct patterns can be observed. In acute hepatitis B, the core IgM, surface antigen, and e antigen are all positive, which is what is seen in this case. At this point, the patient is highly infectious, with viral shedding in body fluids, including saliva. In a late acute infection, core IgG may be positive at the same time as surface and e antigen positivity. In chronic hepatitis B, this same pattern of serologies is seen. If a patient has a prior infection without development of chronic hepatitis, the core IgG and surface antibody is positive. However, when immunity is obtained via vaccination, only the surface antibody (SAb) is positive, the e antigen and surface antigen will be negative since the patient was never infected. The variety of positive antigen-antibody results that can result are outlined in Table VII-70. Acute hepatitis C often is detectable with contemporary immunoassays early during the disease when the aminotransferases are positive. Thus, a positive hepatitis C virus antibody could indicate acute hepatitis C in this individual. However, given his clinical history of prior injection drug use and inability to donate blood, this likely indicates chronic hepatitis C infection. In some instances, ecstasy has been reported to cause drug-induced hepatitis, but given the viral serologies in this patient, this would be unlikely.

TABLE VII-70 Simplified Diagnostic Approach in Patients Presenting with Acute Hepatitis

Serologic Tests of Patient's Serum				
HBsAg	IgM Anti-HAV	IgM Anti-HBc	Anti-HCV	Diagnostic Interpretation
+	−	+	−	Acute hepatitis B
+	−	−	−	Chronic hepatitis B
+	+	−	−	Acute hepatitis A superimposed on chronic hepatitis B
+	+	+	−	Acute hepatitis A and B
−	+	−	−	Acute hepatitis A
−	+	+	−	Acute hepatitis A and B (HBsAg below detection threshold)
−	−	+	−	Acute hepatitis B (HBsAg below detection threshold)
−	−	−	+	Acute hepatitis C

Note: See text for abbreviations.

VII-71. The answer is E. *(Chap. 332)* No treatment is recommended for acute hepatitis B in most individuals because 99% of infected individuals recover without assistance. Therefore, it would not be expected that an individual would derive any particular benefit from treatment. In severe acute hepatitis B, nucleoside analogues, including lamivudine, have been used successfully, although there are no clinical trial data to support such an approach. Hepatitis A is an acute and self-limited illness that does not progress to chronic liver disease. Thus, no treatment is required. Anti–hepatitis A virus Ig can be given prophylactically following a known exposure to prevent development of disease, but it is not helpful in established disease. There is no role for oral or IV corticosteroids in the treatment of acute viral hepatitis of any etiology. It has demonstrated no clinical benefit and may increase the risk of developing chronic disease.

VII-72. The answer is E. *(Chap. 332)* Hepatitis A virus (HAV) is an acute, self-limited virus that is acquired almost exclusively via the fecal-oral route. It is classically a disease of poor hygiene and overcrowding. Outbreaks have been traced to contaminated water, milk, frozen raspberries and strawberries, green onions, and shellfish. Infection occurs mostly in children and young adults. It almost invariably resolves spontaneously and results in lifelong immunity. Fulminant disease occurs in ≤0.1% of cases, and there is no chronic form (in contrast to hepatitis B and C). Diagnosis is made by demonstrating a positive IgM antibody to HAV, as described in this case. An IgG antibody to HAV indicates immunity, obtained by a previous infection or vaccination. A small proportion of patients will experience relapsing hepatitis weeks to months after a full recovery from HAV infection. This too is self-limited. There is no approved antiviral therapy for HAV. An inactivated vaccine has decreased the incidence of the disease, and it is recommended for all U.S. children, for high-risk adults, and for travelers to endemic areas. Passive immunization with Ig is also available, and it is effective in preventing clinical disease before exposure or during the early incubation period.

VII-73. The answer is A. *(Chap. 332)* A clear distinction between viral etiologies of acute hepatitis cannot be made on clinical or epidemiologic features alone. This patient is at risk of many forms of hepatitis due to his lifestyle. Given his occupation in food services, from a public health perspective, it is important to make an accurate diagnosis. Serologies must be obtained to make a diagnosis. Although hepatitis C virus typically does not present as an acute hepatitis, this is not absolute. Hepatitis E virus infects men and women equally and resembles hepatitis A virus in clinical presentation. This patient should be questioned regarding IV drug use, and in addition to hepatitis serologies, an HIV test should be performed.

VII-74. The answer is C. *(Chap. 332)* In HBeAg-expressing transgenic mice, in utero exposure to HBeAg, which is sufficiently small to traverse the placenta, induces T-cell tolerance to both nucleocapsid proteins. This, in turn, may explain why, when infection occurs so early in life, immunologic clearance does not occur, and protracted, lifelong infection ensues. An alternative explanation proposed to explain why robust liver injury does not accompany neonatal HBV infection but predisposes to chronic infection is defective priming of HBV-specific T cells during in utero exposure to HBV. Hepatitis B must cross the placenta for this immune tolerance to occur. Antibodies to hepatitis B core Ag do not confer immunity to infection. Antibodies to hepatitis B Surface Antigen (anti-HBs) confers immunity to infection. Natural killer cells are an important part of the innate immune response in neonates, and likely play an important role in hepatocellular injury in hepatitis B infection.

VII-75. The answer is B. *(Chap. 332)* This patient likely has chronic hepatitis B, as evidenced by the positive HBsAg and the presence of Anti-HBc IgG antibodies. The absence of the e-antigen likely means that she is in a low infectivity state and does not have high levels of viral replication. Table VII-75 shows the common serologic patterns for various hepatitis B disease states.

TABLE VII-75 Commonly Encountered Serologic Patterns of Hepatitis B Infection

HBsAg	Anti-HBs	Anti-HBc	HBeAg	Anti-HBe	Interpretation
+	–	IgM	+	–	Acute hepatitis B, high infectivity[a]
+	–	IgG	+	–	Chronic hepatitis B, high infectivity
+	–	IgG	–	+	1. Late acute or chronic hepatitis B, low infectivity 2. HBeAg-negative ("precore-mutant") hepatitis B (chronic or, rarely, acute)
+	+	+	+/–	+/–	1. HBsAg of one subtype and heterotypic anti-HBs (common) 2. Process of seroconversion from HBsAg to anti-HBs (rare)
–	–	IgM	+/–	+/–	1. Acute hepatitis B[a] 2. Anti-HBc "window"
–	–	IgG	–	+/–	1. Low-level hepatitis B carrier 2. Hepatitis B in remote past
–	+	IgG	–	+/–	Recovery from hepatitis B
–	+	–	–	–	1. Immunization with HBsAg (after vaccination) 2. Hepatitis B in the remote past (?) 3. False positive

[a] IgM anti-HBc may reappear during acute reactivation of chronic hepatitis B.
Note: See text for abbreviations.

VII-76. The answer is E. *(Chap. 332)* There is an effective vaccine against hepatitis E genotype 1 that also has effectiveness against other genotypes. It can be considered in endemic areas. There is no effective vaccine against hepatitis D. Because hepatitis D occurs in the setting of hepatitis B, vaccination against hepatitis B is effective in preventing hepatitis D. It is no longer standard practice to use strict contact isolation precautions for hepatitis A patients since person-to-person transmission is not very common and universal precautions should be sufficient. Serum Ig is not effective in preventing hepatitis C infection after a high-risk exposure. The hepatitis B vaccine contains inactive viral proteins and can be safely administered to immunocompromised patients.

VII-77. The answer is B. *(Chap. 333)* Acetaminophen overdose is the most common cause of acute liver failure and the most common cause of drug-induced liver failure that leads to transplantation. Acetaminophen is metabolized in the liver through two pathways. The primary pathway is a phase II reaction that produces nontoxic sulfate and glucuronide metabolites. The minor pathway occurs through a phase I reaction leading to production of N-acetyl-p-benzoquinone imine (NAPQI). This metabolite is directly toxic to liver cells and can lead to hepatocyte necrosis. With therapeutic use of acetaminophen, glutathione in the liver rapidly converts NAPQI to a nontoxic metabolite that is excreted in the urine. However, glutathione stores can become depleted in the setting of a large acute ingestion, chronic alcoholism, or chronic ingestion of increased acetaminophen. In addition, alcohol upregulates the first enzyme in the metabolic pathway, causing NAPQI to accumulate more quickly in alcoholics. Given the known hepatotoxicity of acetaminophen, the U.S. Food and Drug Administration has recommended a maximum daily dose of no more than 3.25 g, with lower doses in individuals with chronic alcohol use. Acute ingestions of 10–15 g of acetaminophen are sufficient to cause clinical evidence of liver injury, and doses higher than 25 g can lead to fatal hepatic necrosis. The course of illness with acute acetaminophen ingestion follows a predictable pattern. Nausea, vomiting, abdominal pain, and shock occur within 4–12 hours after ingestion. Liver enzymes and synthetic function are normal at this time. Within 24–48 hours, these symptoms subside and are followed by evidence of hepatic injury. Maximal levels of aminotransferases can reach more than 10,000 IU/L and may not occur until 4–6 days after ingestion. These patients must be followed carefully for fulminant hepatic failure with serious complications including encephalopathy, cerebral edema, marked coagulopathy, renal failure, metabolic acidosis, electrolyte abnormalities, and refractory shock. Levels of acetaminophen are predictive of the development of hepatotoxicity. The first level should be measured no sooner than 4 hours after a known ingestion. Levels should be plotted on a nomogram that relates levels to the time after ingestion. If, at 4 hours, the acetaminophen level is greater than 300 μg/mL, significant hepatotoxicity is likely. In the setting of overdose, it may be difficult to know the exact quantity and timing of an ingestion. For the patient presenting in the clinical scenario in this question, her level of >300 μg/mL is quite concerning for a large ingestion, and treatment should be initiated immediately. The primary treatment for acetaminophen overdose is N-acetylcysteine, which acts to replete glutathione levels in the liver and also provides a reservoir of sulfhydryl groups to bind to the toxic metabolites. The typical regimen of N-acetylcysteine is 140 mg/kg given as a loading dose, followed by 70 mg/kg every 4 hours for a total of 15–20 doses. This drug can also be given by continuous infusion. Activated charcoal or cholestyramine should only be given if the patient presents within 30 minutes after ingestion. Hemodialysis will not accelerate clearance of acetaminophen and will not protect the liver. Most patients with fulminant hepatic failure develop acute renal failure, often requiring hemodialysis. If a patient survives an acetaminophen overdose, there is usually no chronic liver injury.

VII-78. **The answer is E.** *(Chap. 333)* Isoniazid (INH) remains central to most antituberculous prophylactic and therapeutic regimens, despite its long-standing recognition as a hepatotoxin. In 10% of patients treated with INH, elevated serum aminotransferase levels develop during the first few weeks of therapy; however, these elevations in most cases are self-limited, mild (values for alanine aminotransferase <200 IU/L), and resolve despite continued drug use. This adaptive response allows continuation of the agent if symptoms and progressive enzyme elevations do not follow the initial elevations. Acute hepatocellular drug-induced liver injury secondary to INH is evident with a variable latency period up to 6 months and is more frequent in alcoholics and patients taking certain other medications, such as barbiturates, rifampin, and pyrazinamide. If the clinical threshold of encephalopathy is reached, severe hepatic injury is likely to be fatal or to require liver transplantation. Liver biopsy reveals morphologic changes similar to those of viral hepatitis or bridging hepatic necrosis. Substantial liver injury appears to be age related, increasing substantially after age 35; the highest frequency is in patients over age 50. Even for patients >50 years of age monitored carefully during therapy, hepatotoxicity occurs in only ~2%, well below the risk estimate derived from earlier experiences. Many public health programs that require INH prophylaxis for a positive tuberculin skin test or QuantiFERON test include monthly monitoring of aminotransferase levels, although this practice has been called into question. Even more effective in limiting serious outcomes may be encouraging patients to be alert for symptoms such as nausea, fatigue, or jaundice, because most fatalities occur in the setting of continued INH use despite clinically apparent illness.

VII-79. **The answer is B.** *(Chap. 333)* Direct toxic hepatitis occurs with predictable regularity after exposure and is dose dependent. The latent period between exposure and liver injury is usually short (often several hours), although clinical manifestations may be delayed for 24–48 hours. Agents producing toxic hepatitis are generally systemic poisons or are converted in the liver to toxic metabolites. The direct hepatotoxins result in morphologic abnormalities that are reasonably characteristic and reproducible for each toxin. Idiosyncratic reactions can produce a variety of liver injury patterns and can be similar to acute viral hepatitis. The occurrence of such reactions is infrequent, unpredictable, and not dose dependent. The incidence of drug-induced liver injury (DILI) is not generally higher in patients with chronic liver injury although the consequences may be more severe. The occurrence of jaundice in phase 3 clinical trials predicts severe hepatotoxicity in a ratio of 10:1 (10 cases of jaundice for every case of severe hepatotoxicity—also called Hy's law after Hyman Zimmerman, a pioneer in the field of DILI).

VII-80. **The answer is C.** *(Chap. 333)* Valproate hepatotoxicity is more common in persons with mitochondrial enzyme deficiencies and may be ameliorated by IV administration of carnitine, which valproate therapy can deplete. Amiodarone liver toxicity can persist for a prolonged period after discontinuation of the drug because of the drug's extremely long half-life. In many patients, hepatic injury from phenytoin is associated with striking fever, lymphadenopathy, rash (Stevens-Johnson syndrome or exfoliative dermatitis), leukocytosis, and eosinophilia, suggesting an immunologically mediated hypersensitivity mechanism. Amoxicillin liver injury is potentiated in the setting of clavulanate for reasons that are unknown. Nitrofurantoin may have a longer latency period to onset of liver injury, in part because of its intermittent and recurrent use.

VII-81. The answer is B. *(Chap. 334)* The patient in this scenario has evidence of chronic active hepatitis B virus (HBV) infection. The presence of hepatitis B e antigen (HBeAg) is indicative of ongoing viral replication, and individuals with HBeAg positivity typically have high levels of HBV DNA on testing. The spectrum of clinical infection in chronic hepatitis B is quite variable, and often, individuals are asymptomatic with elevated liver enzymes identified on testing for other reasons. Thus, the decision to treat chronic HBV infection should not be based on clinical features. Most experts recommend treatment of HBeAg-positive chronic HBV infection with HBV DNA levels >2 × 104 IU/mL if the alanine aminotransferase is elevated greater than twice the upper limit of normal (Table VII-81). To date, the following drugs have been approved for the treatment of chronic HBV: injectable interferon (IFN)-α; pegylated IFN (long-acting IFN bound to polyethylene glycol [PEG IFN]); and the oral agents lamivudine, adefovir dipivoxil, entecavir, telbivudine, and tenofovir. PEG IFN, entecavir, or tenofovir is recommended as first-line therapy. Simeprevir is a protease inhibitor that is approved for the treatment of hepatitis C virus infection. Acyclovir is used to treat herpes simplex viral infections, and ritonavir is a protease inhibitor used to treat HIV infection. The patient's husband should also be screened for HBV given the continued viremia.

VII-82. The answer is B. *(Chap. 334)* Chronic hepatitis develops in about 85% of all individuals affected with hepatitis C virus (HCV), and 20–25% of these individuals will progress to cirrhosis over about 20 years. Among those infected with HCV, about one-third of individuals will have normal or near-normal levels of aminotransferases, although liver biopsy demonstrates active hepatitis in as many as one-half of patients. Moreover, about 25% of individuals with normal aminotransferase levels at one point in time will develop elevations in these enzymes later and can develop progressive liver disease. Thus, normal aminotransferase levels at a single point in time do not definitively rule out the possibility that cirrhosis can develop. Progression to end-stage liver disease in individuals with chronic HCV hepatitis is more likely in older individuals and in patients with longer duration of infection, advanced histologic stage and grade, genotype 1 infection, more complex quasi-species diversity, concomitant other liver disease, HIV infection, and obesity. Among these factors, the best prognostic indicator for the development of progressive liver disease is liver histology. Specifically, patients who have moderate to severe inflammation or necrosis, including septal or bridging fibrosis, have the greatest risk of developing cirrhosis over the course of 10–20 years.

VII-83. The answer is B. *(Chap. 334)* Sofosbuvir and velpatasvir in combination would be the most appropriate first-line agents based on his genotype and current recommendations (Table VII-83). A liver biopsy can provide important prognostic information but with the advent of fibrosis prediction scores and newer imaging modalities, a biopsy is not necessary for most patients prior to initiation of treatment. Ribavirin may be indicated in some combination regimens but its use with pegylated interferon as first-line therapy is no longer common. Both telaprevir and boceprevir are eliminated by and inhibit CYP3A4 so these agents cannot be administered with other medications that induce CYP3A4 or are dependent on CYP3A4 for elimination. Patients with chronic hepatitis C who have detectable HCV RNA in serum, whether or not aminotransferase levels are increased, and chronic hepatitis of any grade and stage are candidates for antiviral therapy with DAA agents. The only exception would be patients with short life expectancies, for whom treating hepatitis C would have no influence on longevity.

TABLE VII-81 Comparison of Pegylated Interferon, Lamivudine, Adefovir, Entecavir, Telbivudine, and Tenofovir Therapy for Chronic Hepatitis B[a]

Feature	PEG IFN[b]	Lamivudine	Adefovir	Entecavir	Telbivudine	Tenofovir
Route of administration	Subcutaneous injection	Oral	Oral	Oral	Oral	Oral
Duration of therapy[c]	48–52 weeks	≥52 weeks	≥48 weeks	≥48 weeks	≥52 weeks	≥48 weeks
Tolerability	Poorly tolerated	Well tolerated	Well tolerated; creatinine monitoring recommended	Well tolerated	Well tolerated	Well tolerated; creatinine monitoring recommended
HBeAg seroconversion						
1 yr Rx	18–20%	16–21%	12%	21%	22%	21%
>1 yr Rx	NA	Up to 50% @ 5 yrs	43% @ 3 yrs[d]	31% @ 2 yrs 44% @ 6 yrs	30% @ 2 yrs	40% @ 5 yrs
Log$_{10}$ HBV DNA reduction (mean copies/mL)						
HBeAg-reactive	4.5	5.5	Median 3.5–5	6.9	6.4	6.2
HBeAg-negative	4.1	4.4–4.7	Median 3.5–3.9	5.0	5.2	4.6
HBV DNA PCR negative (<300–400 copies/mL; <1000 copies/mL for adefovir) at end of yr 1						
HBeAg-reactive	10–25%	36–44%	13–21%	67% (91% @ 4 yrs)	60%	76%
HBeAg-negative	63%	60–73%	48–77%	90%	88%	93%
ALT normalization at end of yr 1						
HBeAg-reactive	39%	41–75%	48–61%	68%	77%	68%
HBeAg-negative	34–38%	62–79%	48–77%	78%	74%	76%
HBsAg loss yr 1	3–4%	≤1%	0%	2%	<1%	3%
>yr 1	12% 5 yr after 1 yr of Rx	No data	5% at yr 5	6% at yr 6	No data	8% at yr 5
Histologic improvement (≥2 point reduction in HAI) at yr 1						
HBeAg-reactive	38% 6 months after	49–62%	53–68%	72%	65%	74%
HBeAg-negative	48% 6 months after	61–66%	64%	70%	67%	72%
Viral resistance	None	15–30% @ 1 yr 70% @ 5 yrs	None @ 1 yr 29% @ 5 yrs	≤1% @ 1 yr[e] 1.2% @ 6 yrs[e]	Up to 5% @ yr 1 Up to 22% @ yr 2	0% @ yr 1 0% through yr 8
Pregnancy category	C	C[f]	C	C	B	B
Cost (US$) for 1 yr	~$18,000	~$2500	~$6500	~$8700[g]	~$6000	~$6000

[a] Generally, these comparisons are based on data on each drug tested individually versus placebo in registration clinical trials; because, with rare exception, these comparisons are not based on head-to-head testing of these drugs, relative advantages and disadvantages should be interpreted cautiously.

[b] Although standard interferon-α administered daily or three times a week is approved as therapy for chronic hepatitis B, it has been supplanted by PEG IFN, which is administered once a week and is more effective. Standard interferon has no advantages over PEG IFN.

[c] Duration of therapy in clinical efficacy trials; use in clinical practice may vary.

[d] Because of a computer-generated randomization error that resulted in misallocation of drug versus placebo during the second year of clinical trial treatment, the frequency of HBeAg seroconversion beyond the first year is an estimate (Kaplan-Meier analysis) based on the small subset in whom adefovir was administered correctly.

[e] Seven percent during a year of therapy (43% at year 4) in lamivudine-resistant patients.

[f] Despite its Class C designation, lamivudine has an extensive pregnancy safety record in women with HIV/AIDS.

[g] Approximately $17,400 for lamivudine-refractory patients.

Abbreviations: ALT, alanine aminotransferase; HAI, histologic activity index; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; NA, not applicable; PEG IFN, pegylated interferon; PCR, polymerase chain reaction; Rx, therapy.

TABLE VII-83 Indications and Recommendations for Antiviral Therapy of Chronic Hepatitis C[a]

Standard Indications for Therapy	**Failed Prior PEG IFN/Ribavirin Therapy, No Cirrhosis**
All patients with chronic HCV infection (detectable HCV RNA, with or without elevated ALT) except for those with short life expectancies because of comorbid conditions. Any stage of fibrosis; highest priority for advanced fibrosis (METAVIR stage 3)/cirrhosis (METAVIR stage 4) (pretreatment biopsy is no longer embraced and has been supplanted by noninvasive measures of fibrosis, e.g., imaging to determine liver elasticity) Responsiveness in groups previously refractory to IFN-based therapy (HIV-HCV co-infection, renal insufficiency, African American and Latino ethnicity, *IL28B* non-C haplotype, obesity, insulin resistance, hepatic decompensation, etc.) is not diminished to contemporary direct-acting oral combination regimens. **Retreatment Recommended** Relapsers, partial responders, or nonresponders after a previous course of IFN-based therapy or prior direct-acting antiviral therapy (see genotype-specific recommendations below). **Antiviral Therapy Not Recommended** Pregnancy: No clinical studies of direct-acting antivirals during pregnancy are available. Ribavirin is contraindicated during pregnancy; therefore, any regimen including ribavirin should not be used. Sofosbuvir; sofosbuvir + ledipasvir; and paritaprevir/ritonavir + ombitasvir + dasabuvir are classified as pregnancy category B, but the other direct-acting antivirals do not have a pregnancy classification. Therefore, these therapies are not indicated routinely in pregnancy and should be used, with caution, only if the benefit of treatment outweighs the potential for fetal risk. **Therapeutic Regimens (based on AASLD-IDSA recommendations, *www.hcvguidelines.org*)**[b] The European Association for the Study of the Liver (EASL) issued recommendations in 2016; divergences from AASLD-IDSA recommendations are summarized as a footnote below.[c]	***Genotype 1a*** **ledipasvir + sofosbuvir 12 weeks** **paritaprevir/ritonavir + ombitasvir + dasabuvir + RBV 12 weeks** **sofosbuvir + simeprevir 12 weeks** **daclatasvir + sofosbuvir 12 weeks** **grazoprevir + elbasvir 12 weeks (without ELB NS5A RASs) or + RBV × 16 weeks (ELB NS5A RASs)** **sofosbuvir + velpatasvir 12 weeks** ***Genotype 1b*** **ledipasvir + sofosbuvir 12 weeks** **paritaprevir/ritonavir + ombitasvir + dasabuvir 12 weeks** **sofosbuvir + simeprevir 12 weeks** daclatasvir + sofosbuvir 12 weeks **grazoprevir + elbasvir 12 weeks** **sofosbuvir + velpatasvir 12 weeks** ***Genotype 2*** **sofosbuvir + velpatasvir 12 weeks** daclatasvir + sofosbuvir 12 weeks ***Genotype 3*** **sofosbuvir + velpatasvir 12 weeks** **daclatasvir + sofosbuvir 12 weeks** ***Genotype 4*** **sofosbuvir + velpatasvir 12 weeks** ledipasvir + sofosbuvir 12 weeks **paritaprevir/r + ombitasvir + RBV 12 weeks (no dasabuvir)** grazoprevir + elbasvir 12 weeks (prior relapse) or + RBV 16 weeks (prior nonresponse) ***Genotypes 5 and 6*** **sofosbuvir + velpatasvir 12 weeks** ledipasvir + sofosbuvir 12 weeks
Treatment-Naïve or Relapsed After Prior PEG IFN/Ribavirin Therapy	**Failed Prior PEG IFN/Ribavirin Therapy, Compensated Cirrhosis**
Genotype 1a **ledipasvir + sofosbuvir 12 weeks (consider 8 weeks for noncirrhotic patients with HCV RNA <6 × 10^6 IU/mL)** **paritaprevir/ritonavir + ombitasvir + dasabuvir + RBV 12 weeks (no cirrhosis) or 24 weeks (cirrhosis)** **sofosbuvir + simeprevir 12 weeks (no cirrhosis) or ± RBV 24 weeks (cirrhosis)** **daclatasvir + sofosbuvir 12 weeks (no cirrhosis) or ± RBV 24 weeks (cirrhosis)** **grazoprevir + elbasvir 12 weeks (no cirrhosis or cirrhosis sans ELB NS5A RASs) or + RBV × 16 weeks (ELB NS5A RASs)** **sofosbuvir + velpatasvir 12 weeks** ***Genotype 1b*** **ledipasvir + sofosbuvir 12 weeks (consider 8 weeks for noncirrhotic patients with HCV RNA <6 × 10^6 IU/mL)** **paritaprevir/ritonavir + ombitasvir + dasabuvir 12 weeks** **sofosbuvir + simeprevir 12 weeks (no cirrhosis) or ± RBV 24 weeks (cirrhosis)** **daclatasvir + sofosbuvir 12 weeks (no cirrhosis) or ± RBV 24 weeks (cirrhosis)** **grazoprevir + elbasvir 12 weeks** **sofosbuvir + velpatasvir 12 weeks** ***Genotype 2*** **sofosbuvir + velpatasvir 12 weeks** daclatasvir + sofosbuvir (no cirrhosis) 12 weeks or 16–24 weeks (cirrhosis)	***Genotype 1a*** **ledipasvir + sofosbuvir + RBV 12 weeks** **ledipasvir + sofosbuvir 24 weeks** **sofosbuvir + velpatasvir 12 weeks** **grazoprevir + elbasvir 12 weeks (without ELB NS5A RASs) or + RBV × 16 weeks (ELB NS5A RASs)** **paritaprevir/ritonavir + ombitasvir + dasabuvir + RBV 24 weeks** sofosbuvir + simeprevir ± RBV 24 weeks (no Q80K variant) daclatasvir + sofosbuvir ± RBV 24 weeks ***Genotype 1b*** **ledipasvir + sofosbuvir + RBV 12 weeks** **ledipasvir + sofosbuvir 24 weeks** **sofosbuvir + velpatasvir 12 weeks** **grazoprevir + elbasvir 12 weeks** **paritaprevir/ritonavir + ombitasvir + dasabuvir 12 weeks** sofosbuvir + simeprevir ± RBV 24 weeks daclatasvir + sofosbuvir ± RBV 24 weeks ***Genotype 2*** **sofosbuvir + velpatasvir 12 weeks** sofosbuvir + daclatasvir 16 or 24 weeks ***Genotype 3*** **sofosbuvir + velpatasvir 12 weeks** daclatasvir + sofosbuvir + RBV 24 weeks ***Genotype 4*** **sofosbuvir + velpatasvir 12 weeks** ledipasvir + sofosbuvir + RBV 12 weeks

(*continued*)

TABLE VII-83 Indications and Recommendations for Antiviral Therapy of Chronic Hepatitis C[a] (*Continued*)

Genotype 3 **sofosbuvir + velpatasvir 12 weeks** **daclatasvir + sofosbuvir 12 weeks (no cirrhosis) or ± RBV 24 weeks (cirrhosis)** ***Genotype 4*** **sofosbuvir + velpatasvir 12 weeks** ledipasvir + sofosbuvir 12 weeks **paritaprevir/r + ombitasvir + RBV 12 weeks (no dasabuvir)** grazoprevir + elbasvir 12 weeks ***Genotypes 5 and 6*** **sofosbuvir + velpatasvir 12 weeks** ledipasvir + sofosbuvir 12 weeks **paritaprevir/ritonavir + ombitasvir + RBV 12 weeks (no dasabuvir)** grazoprevir + elbasvir 12 weeks (prior relapse) or + RBV 16 weeks (prior nonresponse) ledipasvir + sofosbuvir 24 weeks ***Genotypes 5 and 6*** **sofosbuvir + velpatasvir 12 weeks** ledipasvir + sofosbuvir 12 weeks	**Features Associated With Reduced Responsiveness To Direct-Acting Antiviral Combination Therapy** Genotype and subtype (genotype 1a less responsive than genotype 1b for several drugs) Treatment experience Advanced fibrosis (bridging fibrosis, cirrhosis) Reduced adherence

[a] For rapidly evolving new recommendations continue to be issued; for up-to-date treatment recommendations, please see www.hcvguidelines.org.

[b] Class I recommendations in **bold** font, all others are class II recommendations.

[c] The following EASL recommendations differ from those of AASLD-IDSA. (Please note that, although mentioned in EASL recommendations, testing for baseline RASs is not recommended routinely, but, if reliable resistance testing available, results can be used to guide therapy.):

Genotype 1

For genotype 1, simeprevir + sofosbuvir is not recommended.

For genotype 1a, treatment-experienced patients (IFN-based regimen failures) treated with sofosbuvir + ledipasvir should have weight-based ribavirin added. If reliable testing for RASs is available, ribavirin is needed only if baseline RASs are present, and, in such patients, if ribavirin is contraindicated, sofosbuvir + ledipasvir should be extended to 24 weeks.

For genotype 1b, in treatment-naïve, noncirrhotic patients receiving paritaprevir/ritonavir + ombitasvir + dasabuvir a treatment duration of 8 weeks can be considered.

For genotype 1a, in patients treatment with grazoprevir + elbasvir, EASL recommends testing for ELB RASs even in noncirrhotics. If resistance testing is not done, the level of baseline HCV RNA should determine whether ribavirin is added and the duration of therapy. If HCV RNA >800,000 IU/mL, add ribavirin and treat for 16 weeks; if HCV RNA ≤800,000 IU/mL, ribavirin is not added, and treatment for 12 weeks suffices. If baseline testing for RASs is available, patients with HCV RNA >800,000 IU/mL and detectable RASs should be treated with ribavirin for 16 weeks. Treatment without ribavirin and for 12 weeks suffices if HCV RNA ≤800,000 IU/mL even with detectable RASs or even if HCV RNA >800,000 IU/mL with undetectable RASs.

For genotype 1a, in treatment-experienced patients (IFN-based regimen failures) treated with daclatasvir + sofosbuvir, follow the same recommendations described above for ledipasvir + sofosbuvir regarding the addition of ribavirin.

Genotype 2

EASL recommendations are the same as those of AASLD-IDSA.

Genotype 3

For treatment-experienced patients (IFN-based regimen failures) treated with sofosbuvir + velpatasvir or sofosbuvir + daclatasvir, if testing for baseline RASs is not available, add weight-based ribavirin. If resistance testing is available, ribavirin is needed only if baseline RASs are present, and, in such patients, if ribavirin is contraindicated, treatment should be extended to 24 weeks.

Genotype 4

Treatment-experienced patients (IFN-based regimen failures) treated with sofosbuvir + ledipasvir should have weight-based ribavirin added, and, in such patients, if ribavirin is contraindicated, treatment should be extended to 24 weeks.

In treatment-experienced patients (IFN-based regimen failures) treated with grazoprevir + elbasvir, if HCV RNA >800,000 IU/mL, weight-based ribavirin should be added, and treatment should be extended to 16 weeks.

EASL recommends two additional treatment options for genotype 4 (noncirrhotic or cirrhotic) that are not included in AASLD-IDSA guidelines: sofosbuvir + daclatasvir and sofosbuvir + simeprevir. For both these options, treatment-naïve patients should be treated for 12 weeks without ribavirin; treatment-experienced (IFN-based regimen failures) patients should be treated with ribavirin for 12 weeks or, if ribavirin is contraindicated, without ribavirin for 24 weeks.

Genotypes 5 and 6

Treatment-experienced patients (IFN-based regimen failures) treated with sofosbuvir + ledipasvir should have weight-based ribavirin added, and, in such patients, if ribavirin is contraindicated, treatment should be extended to 24 weeks.

EASL recommends an additional treatment option for genotypes 5 and 6 (noncirrhotic or cirrhotic) that is not included in AASLD-IDSA guidelines: sofosbuvir + daclatasvir. Treatment-naïve patients should be treated for 12 weeks without ribavirin; treatment-experienced (IFN-based regimen failures) patients should be treated with ribavirin for 12 weeks or, if ribavirin is contraindicated, without ribavirin for 24 weeks.

Drug doses: sofosbuvir 400 mg; ledipasvir 90 mg; paritaprevir 150 mg; ritonavir 100 mg; ombitasvir 25 mg; dasabuvir 250 mg; ribavirin, weight-based: 1000 mg (<75 kg) to 1200 mg (≥75 kg); simeprevir 150 mg; daclatasvir 60 mg; elbasvir 50 mg; grazoprevir 100 mg; velpatasvir 100 mg.

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; EASL, European Association for the Study of the Liver; ELB NS5A RASs, elbasvir NS5A resistance-associated substitutions; HCV, hepatitis C virus; IFN, interferon; IDSA, Infectious Diseases Society of America; IU, international units (1 IU/mL is equivalent to ~2.5 copies/mL); PEG IFN, pegylated interferon; RASs, resistance-associated substitutions; RBV, ribavirin.

VII-84. The answer is C. *(Chap. 334)* Three types of autoimmune hepatitis have been identified based on clinical and laboratory characteristics. Type I autoimmune hepatitis is typically a disorder seen in young women. The clinical characteristics can be variable from those of chronic hepatitis to fulminant hepatic failure, and many of the features are difficult to distinguish from other causes of chronic hepatitis. In some individuals, extrahepatic manifestations, including fatigue, malaise, weight loss, anorexia, and arthralgias, can be quite prominent. Liver enzymes are elevated but may not correlate with the clinical severity of disease. In more severe cases, elevations in serum bilirubin between 3 and 10 mg/dL can be seen. Hypoalbuminemia occurs in advanced disease, and hypergammaglobulinemia (>2.5 g/dL) is common. The circulating antibody profile in autoimmune hepatitis depends to some extent on the type of hepatitis. Antinuclear antibodies are positive in a homogeneous staining pattern almost invariably in the disease, and rheumatoid factor is also common. Perinuclear antineutrophilic cytoplasmic antibody (p-ANCA) may be positive, but in an atypical fashion. Anti–smooth muscle antibodies and anti-liver/kidney microsomal antibodies are frequently seen, but these are nonspecific because other causes of chronic hepatitis can lead to positivity of these enzymes. Because of the lack of a specific autoimmune profile, the diagnostic criteria for autoimmune hepatitis incorporate a variety of clinical and laboratory features. Specific features that argue against this diagnosis include prominent alkaline phosphatase elevation; presence of mitochondrial antibodies; markers of viral hepatitis; history of hepatotoxic drugs or excess alcohol intake; histologic evidence of bile duct injury; or atypical biopsy features including excess hepatic iron, fatty infiltration, and viral inclusions. Antimitochondrial antibodies are typically seen in primary biliary cirrhosis, not autoimmune hepatitis.

VII-85. The answer is E. *(Chap. 334)* Cellular immune mechanisms appear to be important in the pathogenesis of autoimmune hepatitis. In vitro studies have suggested that in patients with this disorder, CD4+ T lymphocytes are capable of becoming sensitized to hepatocyte membrane proteins and of destroying liver cells. Molecular mimicry by cross-reacting antigens that contain epitopes similar to liver antigens is postulated to activate these T cells, which infiltrate, and result in injury to the liver. Abnormalities of immunoregulatory control over cytotoxic lymphocytes (impaired regulatory CD4+CD25+ T-cell influences) may play a role as well. Circulating autoantibodies are prevalent in patients with autoimmune hepatitis and may aid in diagnosis. However, they have not been firmly linked to direct hepatocyte injury. Immune complex deposition is important in the extrahepatic manifestations of autoimmune hepatitis such as arthralgias, arthritis, cutaneous vasculitis, and glomerulonephritis. Immune complex deposition leads to complement activation, inflammation, and tissue injury.

VII-86. The answer is C. *(Chap. 335)* The pathology of alcoholic liver disease consists of three major lesions, with the progressive injury rarely existing in a pure form: (1) fatty liver, (2) alcoholic hepatitis, and (3) cirrhosis. Fatty liver is present in >90% of daily as well as binge drinkers. A much smaller percentage of heavy drinkers will progress to alcoholic hepatitis, thought to be a precursor to cirrhosis. The prognosis of severe alcoholic liver disease is dismal; the mortality of patients with alcoholic hepatitis concurrent with cirrhosis is nearly 60% at 4 years. Although alcohol is considered a direct hepatotoxin, only between 10 and 20% of alcoholics will develop alcoholic hepatitis. The explanation for this apparent paradox is unclear but involves the complex interaction of facilitating factors, such as drinking patterns, diet, obesity, and gender. There are currently no diagnostic tools that can predict individual susceptibility to alcoholic liver disease. Quantity and duration of alcohol intake are the most important risk factors involved in the development of alcoholic liver disease (Table VII-86). The roles of beverage type(s) (i.e., wine, beer, or spirits) and pattern of drinking (daily vs binge drinking) are less clear. Chronic infection with hepatitis C virus (HCV) is an important comorbidity in the progression of alcoholic liver disease to cirrhosis. Even moderate alcohol intake of 20–50 g/d increases the risk of cirrhosis and hepatocellular cancer in HCV-infected individuals. Patients with both alcoholic liver injury and HCV infection develop decompensated liver disease at a younger age and have poorer overall survival.

TABLE VII-86 Risk Factors for Alcoholic Liver Disease

Risk Factor	Comment
Quantity	In men, 40–80 g/d of ethanol produces fatty liver; 160 g/d for 10–20 years causes hepatitis or cirrhosis Only 15% of alcoholics develop alcoholic liver disease
Gender	Women exhibit increased susceptibility to alcoholic liver disease at amounts >20 g/d; two drinks per day is probably safe
Hepatitis C	Hepatitis C virus infection concurrent with alcoholic liver disease is associated with younger age for severity, more advanced histology, and decreased survival
Genetics	Patatin-like phospholipase domain-containing protein 3 has been associated with alcoholic cirrhosis
Fatty liver	Alcohol injury does not require malnutrition, but obesity and nonalcoholic fatty liver are risk factors Patients should receive vigorous attention to nutritional support

VII-87. **The answer is C.** *(Chap. 335)* This patient presents with severe acute alcoholic hepatitis. In its earliest form, alcoholic liver disease is marked by fatty infiltration of the liver. In more acute alcoholic hepatitis, there is hepatocyte injury with balloon degeneration and necrosis. Many cases of alcoholic hepatitis are asymptomatic. However, as in this case, the severe manifestations can include fever, jaundice, spider nevi, and abdominal pain that can mimic an acute abdomen in its severity. On laboratory examination, the aspartate aminotransferase is typically elevated more than the alanine aminotransferase, although the total transaminase levels are rarely greater than 400 IU/L. Hyperbilirubinemia can be quite marked with lesser elevation in alkaline phosphatase. Hypoalbuminemia and coagulopathy are poor prognostic indicators. A discriminate function (DF) can be calculated as follows: (4.6 Å~ the prolongation of prothrombin time above control) + serum bilirubin. A DF >32 is associated with poor prognosis and is an indication for treatment of acute alcoholic hepatitis. The model for end-stage liver disease score can also be used for prognostication in acute alcoholic hepatitis, with a score greater than 21 being an indication for treatment as well. This patient has a DF of >80, indicating very severe disease and a poor prognosis. Complete abstinence from alcohol is imperative. Treatment with prednisone 40 mg daily (or prednisolone 32 mg daily) for 4 weeks should be initiated. Following the initial period, a taper should be achieved over a period of 4 weeks. The role of tumor necrosis factor (TNF)-α expression and receptor activity in alcoholic liver injury has led to an examination of TNF inhibition as an alternative to glucocorticoids for severe alcoholic hepatitis. The nonspecific TNF inhibitor pentoxifylline (400 mg three times daily for 4 weeks) demonstrated improved survival in the therapy of severe alcoholic hepatitis, primarily due to a decrease in hepatorenal syndrome. Monoclonal antibodies that neutralize serum TNF-α should not be used in alcoholic hepatitis because of studies reporting increased deaths secondary to infection and renal failure. Liver transplantation is an accepted indication for treatment in selected and motivated patients with end-stage cirrhosis. Outcomes are equal or superior to other indications for transplantation.

VII-88. **The answer is C.** *(Chap. 335)* Alcoholic fatty liver was once thought to be relatively benign, but in the presence of features such as giant mitochondria, perivenular fibrosis, and macrovesicular fat it may be associated with progressive liver injury. Fatty accumulation begins in the perivenular hepatocytes and can eventually involve the entire hepatic lobule. Ballooning degeneration, spotty necrosis, polymorphonuclear infiltrate, and fibrosis in the perivenular and perisinusoidal space of Disse are hallmarks of alcoholic hepatitis. The changes of both alcoholic fatty liver disease and alcoholic hepatitis are reversible after the cessation of drinking. It can be hard to differentiate alcoholic from nonalcoholic fatty liver disease. A careful drinking history is essential to identifying alcohol as a risk factor.

VII-89. **The answer is C.** *(Chap. 336)* At present, there are no Food and Drug Administration-approved therapies for the treatment of nonalcoholic fatty liver disease (NAFLD). Thus, the current approach to NAFLD management focuses on treatment to improve the risk factors for nonalcoholic steatohepatitis (NASH; i.e., obesity, insulin resistance, metabolic syndrome, dyslipidemia). Based on our understanding of the natural history of NAFLD, only patients with NASH or those with features of hepatic fibrosis on liver biopsy are considered currently for targeted pharmacologic therapies. Lifestyle changes and dietary modification are the foundation for NAFLD treatment. Many studies indicate that lifestyle modification can improve serum aminotransferases and hepatic steatosis, with loss of at least 3–5% of body weight improving steatosis, but greater weight loss (up to 10%) necessary to improve steatohepatitis. The benefits of different dietary macronutrient content (e.g., low-carbohydrate vs low-fat diets, saturated vs unsaturated fat diets) and different intensities of calorie restriction appear to be comparable. In adults with NAFLD, exercise regimens that improve fitness may be sufficient to reduce hepatic steatosis, but their impact on other aspects of liver histology remains unknown. Antioxidants have also been evaluated for the treatment of NAFLD because oxidant stress is thought to contribute to the pathogenesis of NASH. Vitamin E, an inexpensive yet potent antioxidant, has been examined in several small pediatric and adult studies with varying results. In all of those studies, vitamin E was well tolerated, and most showed modest improvements in aminotransferase levels, radiographic features of hepatic steatosis, and/or histologic features of NASH. Statins are an important class of agents to treat dyslipidemia and decrease cardiovascular risk. There is no evidence to suggest that statins cause liver failure in patients with any chronic liver disease, including NAFLD. The incidence of liver enzyme elevations in NAFLD patients taking statins is also no different than that of healthy controls or patients with other chronic liver diseases. Moreover, several studies have suggested that statins may improve aminotransferases and histology in patients with NASH. However, there is continued reluctance to use statins in patients with NAFLD. The lack of evidence that statins harm the liver in NAFLD patients, combined with the increased risk for cardiovascular morbidity and mortality in NAFLD patients, warrants the use of statins to treat dyslipidemia in patients with NAFLD/NASH. Although interest in bariatric surgery as a treatment for NAFLD exists, a recently published *Cochrane Review* concluded that lack of randomized clinical trials or adequate clinical studies prevents definitive assessment of benefits and harms of bariatric surgery as a treatment for NASH. Most studies of bariatric surgery have shown that it is generally safe in individuals with well-compensated chronic liver disease and improves hepatic steatosis and necroinflammation (i.e., features of NAFLD/NASH); however, effects on hepatic fibrosis have been variable.

VII-90. **The answer is A.** *(Chap. 336)* In some studies up to 25% of Americans have hepatic steatosis on imaging. About 25% of patients with nonalcoholic fatty liver disease (NAFLD) will go on to develop nonalcoholic steatohepatitis (NASH), which can lead to cirrhosis. By some estimates, NAFLD will be the most common indication for liver transplant in the next decade. Insulin resistance, in large part secondary to obesity, is a big driver of NAFLD and NASH, as insulin stimulates lipid uptake, fat synthesis, and fat storage leading to triglyceride accumulation in hepatocytes. The triglycerides themselves are not hepatotoxic. However, their precursors (e.g., fatty acids and diacylglycerols) and metabolic by-products (e.g., reactive oxygen species) may damage hepatocytes, leading to hepatocyte lipotoxicity. Lipotoxicity also triggers the generation of other factors (e.g., inflammatory cytokines, hormonal mediators) that deregulate systems that normally maintain hepatocyte viability. The net result is increased hepatocyte death. There are no serum biomarkers that can reliably make the diagnosis of NASH. In NAFLD the levels of serum aminotransferases (aspartate aminotransferase and alanine aminotransferase) do not reliably reflect the severity of liver cell injury, extent of liver cell death, or related liver inflammation and fibrosis. Thus, they are imperfect for determining which individuals with NAFLD have NASH.

VII-91. **The answer is B.** *(Chap. 337)* Spontaneous bacterial peritonitis (SBP) is a common and severe complication of ascites characterized by spontaneous infection of the ascitic fluid without an intra-abdominal source. In patients with cirrhosis and ascites severe enough for hospitalization, SBP can occur in up to 30% of individuals and can have a 25% in-hospital mortality rate. Bacterial translocation is the presumed mechanism for development of SBP, with gut flora traversing the intestine into mesenteric lymph nodes, leading to bacteremia and seeding of the ascitic fluid. The most common organisms are *Escherichia coli* and other gut bacteria; however, gram-positive bacteria, including *Streptococcus viridans, Staphylococcus aureus, and Enterococcus* spp., can also be found. If more than two organisms are identified, secondary bacterial peritonitis due to a perforated viscus should be considered. The diagnosis of SBP is made when the fluid sample has an absolute neutrophil count >250/μL. In this case, the patient has an absolute neutrophil count of 320/μL (800 × 0.4), and, therefore, has SBP. Patients with ascites may present with fever, altered mental status, elevated white blood cell count, and abdominal pain or discomfort, or they may present without any of these features. Therefore, it is necessary to have a high degree of clinical suspicion, and peritoneal taps are important for making the diagnosis. Treatment is with a second-generation cephalosporin, with cefotaxime as the most commonly used antibiotic. In patients with variceal hemorrhage, the frequency of SBP is significantly increased, and prophylaxis against SBP is recommended when a patient presents with upper gastrointestinal bleeding. Furthermore, in patients who have had an episode(s) of SBP and recovered, once-weekly administration of antibiotics is used as prophylaxis for recurrent SBP. There is no indication for hemodialysis with the normal serum creatine or esophagogastroduodenoscopy with no history of bleeding and a stable hemoglobin. Blood urea nitrogen (BUN) may increase as a result of the infection. Similarly, although the BUN is elevated and the patient has altered mental status, lactulose would not treat the primary disorder causing the altered mental status. Given the likely diagnosis of SBP, empiric therapy for meningitis is not warranted at this time.

VII-92. **The answer is C.** *(Chap. 337)* The clinical presentation is consistent with a cholestatic picture, which can present with painless jaundice and pruritus. The pruritus can be prominent and is present in 50% of individuals at the time of diagnosis. The pruritus is typically intermittent and worse in the evening. There is no other prominent association, such as following hot baths or showers, which occurs in polycythemia vera. Other causes of pruritus outside of cholestasis include lymphoma and uncontrolled hypo- or hyperthyroidism. However, the laboratory studies in this patient clearly represent cholestasis with an elevation in alkaline phosphatase and bilirubin. The clinical characteristics are more commonly seen in primary biliary cirrhosis compared with primary sclerosis cholangitis as the patient is a middle-aged female with positive antimitochondrial antibodies. In contrast, primary sclerosing cholangitis is associated with positive perinuclear antineutrophil cytoplasmic antibodies in 65% of patients, and 50% of individuals with primary sclerosing cholangitis have a history of ulcerative colitis.

VII-93. **The answer is A.** *(Chap. 337)* The cornerstone of the management of ascites is sodium restriction to less than 2 g daily. A common misconception is to institute a fluid restriction as well. However, this is neither effective nor necessary. With a sodium restriction to 2 g daily, most mild ascites can be managed quite well. If sodium restriction alone fails to correct ascites, then initiation of diuretics is required. Spironolactone at a dose of 100–200 mg daily is the initial diuretic used for ascites and can be titrated as high as 400–600 mg daily if tolerated. Loop diuretics can be added to spironolactone. The typical agent is furosemide beginning at 40–80 mg daily with maximum doses of about 120–160 mg daily. Care must be taken to avoid renal dysfunction with loop diuretics, and higher doses may not be tolerated. If ascites is refractory to these treatments, transjugular intrahepatic portosystemic shunt (TIPS) can be considered. This procedure creates a direct portocaval shunt by introducing an expandable metal stent from the hepatic veins through the substance of the liver into the portal veins. Thus, TIPS decreases portal pressure, which in turn should decrease ascites and the risk of variceal bleeding. However, hepatic encephalopathy typically worsens following TIPS.

VII-94. **The answer is B.** *(Chap. 337)* The presence of cirrhosis in an elderly woman with no prior risk factors for viral or alcoholic cirrhosis should raise the possibility of primary biliary cirrhosis (PBC). PBC is characterized by chronic inflammation and fibrous obliteration of intrahepatic ductules. The cause is unknown, but autoimmunity is assumed because there is an association with other autoimmune disorders, such as autoimmune thyroiditis, CREST (**c**alcinosis, **R**aynaud's phenomenon, **e**sophageal dysmotility, **s**clerodactyly, telangiectasia) syndrome, and sicca syndrome. The vast majority of patients with symptomatic disease are women. The antimitochondrial antibody (AMA) test is positive in over 90% of patients with PBC and only rarely is positive in other conditions. This makes it the most useful initial test in the diagnosis of PBC. Because there are false-positive results, if AMA is positive, a liver biopsy is performed to confirm the diagnosis. The 24-hour urine copper collection is useful in the diagnosis of Wilson disease. Hepatic failure from Wilson disease typically occurs before age 50 years. Hemochromatosis may result in cirrhosis. It is associated with lethargy, fatigue, loss of libido, discoloration of the skin, arthralgias, diabetes, and cardiomyopathy. Ferritin levels are usually increased, and the most suggestive laboratory abnormality is an elevated transferrin saturation percentage. Although hemochromatosis is a possible diagnosis in this case, PBC is more likely in light of the clinical scenario. Although chronic hepatitis B and hepatitis C are certainly in the differential diagnosis and must be ruled out, they are unlikely because of the patient's history and lack of risk factors.

VII-95. **The answer is B.** *(Chap. 337)* Infection is probably the most common, and the most concerning cause of worsening hepatic encephalopathy in a patient with known liver disease. Dehydration and electrolyte abnormalities are common causes of hepatic encephalopathy. Dehydration can lead to a contraction alkalosis that causes more ammonium ions (NH_4^+) to become NH_3, which can more easily cross the blood-brain barrier to provoke encephalopathy. Hypokalemia can have the same effect. Hyperkalemia would be associated with the extracellular shifting of hydrogen ions and have the opposite effect, and therefore is less likely. Hyponatremia can directly cause altered mental status but can also be associated with dehydration, both of which can worsen encephalopathy. Medication nonadherence is a common cause of worsening hepatic encephalopathy.

VII-96. **The answer is D.** *(Chap. 337)* The approach to patients once they have had a variceal bleed is first to treat the acute bleed, which can be life-threatening, and then to prevent further bleeding. The medical management of acute variceal hemorrhage includes the use of vasoconstricting agents, usually somatostatin or octreotide. Balloon tamponade (Sengstaken-Blakemore tube or Minnesota tube) can be used in patients who cannot receive endoscopic therapy immediately or who need stabilization prior to endoscopic therapy. Endoscopic intervention is used as first-line treatment to control bleeding acutely. Some endoscopists will use variceal injection therapy (sclerotherapy) as initial therapy, particularly when bleeding is vigorous. Variceal band ligation is used to control acute bleeding in over 90% of cases and should be repeated until obliteration of all varices is accomplished. When esophageal varices extend into the proximal stomach, band ligation is less successful. In these situations, when bleeding continues from gastric varices, consideration for transjugular intrahepatic portosystemic shunt (TIPS) should be made. This offers an alternative to surgery for acute decompression of portal hypertension. Encephalopathy can occur in as many as 20% of patients after TIPS and is particularly problematic in elderly patients and in patients with pre-existing encephalopathy. TIPS should be reserved for individuals who fail endoscopic or medical management or who are poor surgical risks. TIPS can sometimes be used as a bridge to transplantation. Beta blockers, such as propranolol and nadolol, have been shown to decrease the risk of recurrent variceal bleeding and reduce mortality from a subsequent bleed but should not be used in the setting of an acutely bleeding patient.

VII-97. **The answer is B.** *(Chap. 337)* Prevention of further or subsequent variceal bleeding can be accomplished with repeated variceal band ligation until varices are obliterated. Nonselective beta blockers, such as propranolol and nadolol, have been shown to decrease the risk of recurrent variceal bleeding and reduce mortality from a subsequent bleed. Their efficacy is lessened once the esophageal varices have been banded, but they can be useful to treat portal hypertensive gastropathy that is not directly treated with variceal ligation. A TIPS would reduce portal pressure and lead to a reduction in recurrent variceal bleeding. Transplant would likewise restore normal portal pressure and lead to resolution of existing varices. A continuous infusion of octreotide may promote splanchnic vasoconstriction and can be used to manage acute variceal bleeding. Subcutaneous octreotide is not used as a prophylactic treatment.

VII-98. The answer is B. *(Chap. 337)* Cessation of drinking markedly improves survival in patients with alcoholic cirrhosis and there is evidence that fibrosis can improve after cessation. Alcoholic cirrhosis is usually "micronodular" (<3 mm) but with the cessation of drinking larger nodules may form. Alcohol is the second most common cause of cirrhosis in the United States, behind hepatitis C. Pentoxifylline is an oral agent that reduces production of tumor necrosis factor (TNF)-α and has been used in the treatment of acute alcoholic hepatitis. Recent studies have used parenterally administered inhibitors of TNF-α such as infliximab or etanercept for the treatment of alcoholic hepatitis. Early results have shown no adverse events; however, there was no clear-cut improvement in survival for acute hepatitis or cirrhosis.

VII-99. The answer is D. *(Chap. 337)* Hepatorenal syndrome (HRS) is caused by a combination of increased renovascular constriction and reduced effective circulatory volume. The use of diuretics would potentially worsen renal perfusion and could precipitate worsening renal failure. A number of treatments have been tried in the setting of HRS with limited efficacy including IV albumin along with midodrine and octreotide. Most patients will recover renal function if they undergo liver transplantation. It is always advisable to consider a wide range of potential causes for renal failure in patients with chronic liver disease.

VII-100. The answer is D. *(Chap. 338)* Patients with fulminant hepatic failure are highest priority for cadaveric liver transplantation. Currently in the United States, all donor livers are distributed through a nationwide organ-sharing network (United Network for Organ Sharing) designed to allocate available organs based on regional considerations and recipient acuity. Recipients who have the highest disease severity generally have the highest priority, but allocation strategies that balance highest urgency against best outcomes continue to evolve to distribute cadaver organs most effectively. Allocation is based on the model for end-stage liver disease (MELD) score, which is based on a mathematical model that includes bilirubin, creatinine, and international normalized ratio. Neither waiting time (except as a tiebreaker between two potential recipients with the same MELD scores) nor posttransplantation outcome is taken into account. Use of the MELD score has been shown to reduce waiting list mortality, to reduce waiting time prior to transplantation, and to be the best predictor of pretransplantation mortality. The highest priority (status 1) for liver transplantation continues to be reserved for patients with fulminant hepatic failure or primary graft nonfunction.

VII-101. The answer is B. *(Chap. 338)* Several conditions receive a disease-specific model for end-stage liver disease exception, which allows patients to receive a liver when they might not be as clinically ill. Such conditions include hepatocellular carcinoma, portopulmonary hypertension, hepatopulmonary syndrome, familial amyloid polyneuropathy, primary hyperoxaluria (necessitating liver-kidney transplantation), cystic fibrosis liver disease, and highly selected cases of hilar cholangiocarcinoma. ABO incompatibility and preformed cytotoxic human leukocyte antigen antibodies are not contraindications to transplant. HIV patients have successfully undergone liver transplantation. While living donor transplants have increased the number of potential donors, the procedure comes with several important risks to the donor including biliary complications in ~5%; postoperative complications such as wound infection, small-bowel obstruction, and incisional hernias in 9–19%, and, even death in 0.2–0.4%.

VII-102. The answer is B. *(Chap. 339)* In the National Health and Nutrition Examination Survey, the prevalence of gallstone disease in the United States was 7.9% in men and 16.6% in women. Although the disease is quite prevalent, not all patients with gallstone disease require cholecystectomy. It is estimated that 1–2% of patients with asymptomatic gallstone disease will develop complications that will require surgery yearly. Therefore, it is important to know which patients with asymptomatic gallstones require referral for surgery. The first factor to consider is whether the patient has symptoms that are caused by gallstones and are frequent enough and severe enough to necessitate surgery. Commonly called biliary colic, the classic symptoms of gallstone disease are right upper quadrant pain and fullness that begins suddenly and can last as long as 5 hours. Nausea and vomiting can accompany the episode. Vague symptoms of epigastric fullness, dyspepsia, and bloating following meals should not be considered biliary colic. A second factor that would be considered in recommending a patient for cholecystectomy is whether the patient has a prior history of complications of gallstone disease such as pancreatitis or acute cholecystitis. A final factor that would lead to the recommendation for cholecystectomy is the presence of anatomical factors that would increase the likelihood of complications such as a porcelain gallbladder or congenital abnormalities of the biliary tract. Individuals with very large stones (>3 cm) would also need to be considered carefully for cholecystectomy. Ursodeoxycholic acid can be used in some instances to dissolve gallstones. It acts to decrease the cholesterol saturation of bile and also allows dispersion of cholesterol from stones by producing a lamellar crystalline phase. However, it is only effective in individuals with radiolucent stones measuring less than 10 mm.

VII-103. **The answer is D.** *(Chap. 339)* A practitioner needs to have a high index of suspicion for acalculous cholecystitis in critically ill patients who develop decompensation during the course of treatment for the underlying disease and have no other apparent source of infection. Some predisposing conditions for the development of acalculous cholecystitis include serious trauma or burns, postpartum following prolonged labor, prolonged parenteral hyperalimentation, and during the postoperative period following orthopedic and other major surgical procedures. The clinical manifestations of acalculous cholecystitis are identical to calculous disease, but the disease is more difficult to diagnose. Ultrasonography and CT scanning typically only show biliary sludge, but they may demonstrate large and tense gallbladders. Hepatobiliary scintigraphy often shows delayed or absent gallbladder emptying. Successful management relies on accurate and early diagnosis. In critically ill patients, a percutaneous cholecystostomy may be the safest immediate procedure to decompress an infected gallbladder. Once the patient is stabilized, early elective cholecystectomy should be considered. Metronidazole to provide anaerobic coverage should be added, but this would not elucidate or adequately treat the underlying condition.

VII-104. **The answer is B.** *(Chaps. 45 and 339)* The clinical presentation is consistent with a cholestatic picture. Painless jaundice always requires an extensive workup, as many of the underlying pathologies are ominous and early detection and intervention often offers the only hope for a good outcome. In this case, the gallbladder showed no evidence of stones, and the patient shows no evidence of clinical cholecystitis, and so a hepatobiliary iminodiacetic acid scan is not indicated. Similarly, antibiotics are not necessary at this point. The cholestatic picture without significant elevation of the transaminases on the liver function tests makes acute hepatitis unlikely. Antimitochondrial antibodies are elevated in cases of primary biliary cirrhosis (PBC), which may present in a similar fashion. However, PBC is far more common in women than in men, and the average age of onset is the fifth or sixth decade. The lack of an obvious lesion on CT scan does not rule out a source of the cholestasis in the biliary tree. Malignant causes, such as cholangiocarcinoma and tumor of the ampulla of Vater, and nonmalignant causes, such as sclerosing cholangitis and Caroli disease, may be detected only by direct visualization with endoscopic retrograde cholangiopancreatography (ERCP). ERCP is useful both diagnostically and therapeutically as stenting procedures may be done to alleviate the obstruction.

VII-105. **The answer is E.** *(Chap. 339)* Approximately 10–20% of persons with rapid weight reduction achieved through very-low-calorie dieting develop gallstones. An excess of biliary cholesterol in relation to bile acids and phospholipids promotes the formation of unstable, cholesterol-rich vesicles in which cholesterol crystals can form. The most important factor in cholesterol stone formation is increased biliary secretion of cholesterol. This may occur in association with obesity, the metabolic syndrome, high-caloric and cholesterol-rich diets, or drugs (e.g., clofibrate) and may result from increased activity of hydroxymethylglutaryl-coenzyme A reductase, the rate-limiting enzyme of hepatic cholesterol synthesis, and increased hepatic uptake of cholesterol from blood. Gallbladder hypomotility is an important risk factor for stone formation. If the gallbladder empties all supersaturated or crystal containing bile completely, stones are not able to grow. Nucleation of cholesterol monohydrate crystals is greatly accelerated in human lithogenic bile and is an important factor in stone formation.

VII-106. The answer is D. *(Chap. 339)* Cholecystectomy is a very successful operation that provides total or near-total relief of preoperative symptoms in 75–90% of patients. The optimal timing of surgical intervention in patients with acute cholecystitis depends on stabilization of the patient. The clear trend is toward earlier surgery, and this is due in part to requirements for shorter hospital stays. Urgent (emergency) cholecystectomy or cholecystostomy is probably appropriate in most patients in whom a complication of acute cholecystitis such as empyema, emphysematous cholecystitis, or perforation is suspected or confirmed. Patients with uncomplicated acute cholecystitis should undergo early elective laparoscopic cholecystectomy, ideally within 48–72 hours after diagnosis. The complication rate is not increased in patients undergoing early as opposed to delayed (>6 weeks after diagnosis) cholecystectomy. Unsuspected common bile duct stones are left behind in approximately 1–5% of cholecystectomy patients. The incidence of common bile duct stones increases with increasing age of the patient, so that up to 25% of elderly patients may have calculi in the common duct at the time of cholecystectomy.

VII-107. The answer is C. *(Chap. 339)* IgG4-associated cholangitis is a recently described biliary disease of unknown etiology that presents with biochemical and cholangiographic features indistinguishable from primary sclerosing cholangitis (PSC), is often associated with autoimmune pancreatitis and other fibrosing conditions, and is characterized by elevated serum IgG4 and infiltration of IgG4-positive plasma cells in bile ducts and liver tissue. All newly diagnosed PSC patients should have a serum IgG4 level checked. In contrast to PSC, IgG4-associated cholangitis is not associated with inflammatory bowel disease and should be suspected if associated with increased serum IgG4 and unexplained pancreatic disease. Viral infections such as HIV can lead to biliary pathology. In patients with AIDS, cholangiopancreatography may demonstrate a broad range of biliary tract changes as well as pancreatic duct obstruction and occasionally pancreatitis. Further, biliary tract lesions in AIDS include infection and cholangiopancreatography changes similar to those of PSC.

VII-108. The answer is D. *(Chap. 340)* Ruptured ectopic pregnancy has been associated with a rise in serum amylase but pregnancy in and of itself is not a common cause of elevated amylase. Table VII-108 lists common conditions associated with an elevated amylase level.

VII-109. The answer is B. *(Chap. 340)* Endoscopic ultrasound (EUS) and magnetic resonance cholangiopancreatography (MRCP) have replaced endoscopic retrograde cholangiopancreatography (ERCP) for diagnostic purposes. EUS allows one to obtain information about the pancreatic duct as well as the parenchyma and has few procedure-related complications associated with it, in contrast to the 5–10% of post-ERCP pancreatitis observed. MRI and MRCP are now being used to view the bile ducts, pancreatic duct, and the pancreas parenchyma in both acute pancreatitis and chronic pancreatitis. EUS has been studied as a diagnostic modality for chronic pancreatitis. Criteria for abnormalities on EUS in severe chronic pancreatic disease have been developed. There is general agreement that the presence of five or more of the nine criteria listed in Table VII-109 is highly predictive of chronic pancreatitis. Abdominal CT is not necessary to make the diagnosis of acute pancreatitis but can detect pancreatic necrosis. Plane radiographs have no real role in the diagnostic evaluation of pancreatic disease. Abdominal ultrasound can be helpful in the initial workup of abdominal pain and acute pancreatitis, but image quality can be limited by the presence of overlying bowel gas.

TABLE VII-108 **Causes of Hyperamylasemia and Hyperamylasuria**

Pancreatic Disease
I. Pancreatitis
A. Acute
B. Chronic: ductal obstruction
C. Complications of pancreatitis
1. Pancreatic pseudocyst
2. Ascites caused by pancreatic duct disruption
3. Pancreatic necrosis
II. Pancreatic trauma
III. Pancreatic carcinoma
Nonpancreatic Disorders
I. Renal insufficiency
II. Salivary gland lesions
A. Mumps
B. Calculus
C. Irradiation sialadenitis
D. Maxillofacial surgery
III. “Tumor” hyperamylasemia
A. Carcinoma of the lung, esophagus, breast, or ovary
IV. Macroamylasemia
V. Burns
VI. Diabetic ketoacidosis
VII. Pregnancy
VIII. Renal transplantation
IX. Cerebral trauma
X. Drugs: opiates
Other Abdominal Disorders
I. Biliary tract disease: cholecystitis, choledocholithiasis
II. Intraabdominal disease
A. Perforated or penetrating peptic ulcer
B. Intestinal obstruction or inflammation
C. Ruptured ectopic pregnancy
D. Peritonitis
E. Aortic aneurysm
F. Postoperative hyperamylasemia

TABLE VII-109 **Endoscopic Ultrasonographic Criteria for Chronic Pancreatitis (Total Criteria = 9)**

Ductal	Parenchymal
Stones	Echogenic strands
Hyperechoic main duct margins	Echogenic foci
Main duct irregularity	Lobular contour
Main duct dilatation	Cyst
Visible side branches	

VII-110. **The answer is A.** *(Chap. 341)* All pancreatic enzymes have pH optima in the alkaline range. The proteolytic pancreatic enzymes are secreted as inactive zymogen precursors. Enterokinase, an enzyme found in the duodenal mucosa, cleaves the lysine-isoleucine bond of trypsinogen to form trypsin. Trypsin then activates the other proteolytic zymogens and phospholipase A2 in a cascade phenomenon. The stimulatory neurotransmitters are acetylcholine and gastrin-releasing peptides. These neurotransmitters activate calcium-dependent secondary messenger systems, resulting in the release of zymogens into the pancreas duct. In contrast to other species, there are no cholecystokinin (CCK) receptors on acinar cells in humans. CCK in physiologic concentrations stimulates pancreatic secretion by stimulating afferent vagal and intrapancreatic nerves.

VII-111. The answer is A. *(Chap. 341)* In combination with a consistent clinical story and radiographic findings, serum amylase and lipase values threefold or more above normal virtually clinch the diagnosis of acute pancreatitis. Gut perforation, ischemia, and infarction should be excluded. Serum lipase is the preferred test and has a higher specificity than serum amylase. There is no correlation between the severity of pancreatitis and the degree of serum lipase and amylase elevations. After 3–7 days, even with continuing evidence of pancreatitis, total serum amylase values tend to return toward normal. However, pancreatic isoamylase and lipase levels may remain elevated for 7–14 days. Elevation of serum amylase is not specific for acute pancreatitis; notably, patients with metabolic academia (e.g., diabetic ketoacidosis) may have spurious elevation of serum amylase without pancreatitis. Hypocalcemia occurs in approximately 25% of cases of acute pancreatitis, whereas hypercalcemia is not a feature.

VII-112. The answer is A. *(Chap. 341)* The most common cause of acute pancreatitis in the United States is gallstones causing common bile duct obstruction. Although bile duct obstruction may be demonstrated on technetium hepatobiliary iminodiacetic acid scan, right upper quadrant ultrasound is preferred for ease, demonstration of gallstones in the gallbladder, and demonstration of obstructed bile duct. Alcohol is the second most common cause of acute pancreatitis, followed by complications of endoscopic retrograde cholangiopancreatography. Hypertriglyceridemia accounts for 1–4% of cases of acute pancreatitis with triglyceride levels usually >1000 mg/dL. Other potential common causes include trauma, surgery, drugs such as valproic acid, anti-HIV medications, estrogens, and sphincter of Oddi dysfunction. Additionally, a number of rare causes have been described. The most judicious first step in evaluation of acute pancreatitis is to test for gallstones and pursue more rare causes after the most common cause has been ruled out.

VII-113. The answer is B. *(Chap. 341)* Blue-red-purple or green-brown discoloration of the flanks (Turner sign) reflects tissue catabolism of hemoglobin from severe necrotizing pancreatitis with hemorrhage. A faint blue discoloration around the umbilicus (Cullen sign) may also occur as the result of hemoperitoneum. While a ruptured ectopic pregnancy could present with hemoperitoneum, the patient’s age and other clinical history makes alcoholic pancreatitis a much more likely diagnosis. Pancreatic calcification on abdominal plain films would suggest possible chronic pancreatitis. Endoscopic ultrasound plus magnetic resonance cholangiopancreatography have become common in the diagnosis of pancreatic disease but would probably not be indicated at this time given that the patient’s history and physical examination indicated likely severe necrotizing pancreatitis from alcohol abuse,

VII-114. The answer is B. *(Chap. 341)* Any severe acute pain in the abdomen or back should suggest the possibility of acute pancreatitis. The diagnosis is established by two of the following three criteria: (1) typical abdominal pain in the epigastrium that may radiate to the back, (2) threefold or greater elevation in serum lipase and/or amylase, and (3) confirmatory findings of acute pancreatitis on cross-sectional abdominal imaging. Many patients with acute pancreatitis have concomitant hypoxemia and may even develop acute respiratory distress syndrome, but hypoxemia is not a diagnostic criterion for acute pancreatitis.

VII-115. The answer is A. *(Chap. 341)* An elevated hematocrit at presentation in patients with acute pancreatitis is associated with a worse outcome in patients as it reflects significant hemoconcentration from vascular leakage and third spacing. A failure of the hematocrit to drop after the first 12–24 hours of fluid resuscitation is also a poor prognostic sign and could indicate the need for more intensive monitoring in the intensive care unit. This patient’s drop in hematocrit most likely represents a favorable response to initial fluid resuscitation.

VII-116. The answer is A. *(Chap. 341)* The initial phase of acute pancreatitis is characterized by intrapancreatic digestive enzyme activation and acinar cell injury. Trypsin activation appears to be mediated by lysosomal hydrolases such as cathepsin B that become colocalized with digestive enzymes in intracellular organelles; it is currently believed that acinar cell injury is the consequence of trypsin activation. The second phase of pancreatitis involves the activation, chemoattraction, and sequestration of leukocytes and macrophages in the pancreas, resulting in an enhanced intrapancreatic inflammatory reaction. Neutrophil depletion induced by prior administration of an antineutrophil serum has been shown to reduce the severity of experimentally induced pancreatitis. There is also evidence to support the concept that neutrophils can activate trypsinogen. Thus, intrapancreatic acinar cell activation of trypsinogen could be a two-step process (i.e., an early neutrophil-independent and a later neutrophil-dependent phase). The third phase of pancreatitis is due to the effects of activated proteolytic enzymes and cytokines, released by the inflamed pancreas, on distant organs. Activated proteolytic enzymes, especially trypsin, not only digest pancreatic and peripancreatic tissues but also activate other enzymes such as elastase and phospholipase A2. The active enzymes and cytokines then digest cellular membranes and cause proteolysis, edema, interstitial hemorrhage, vascular damage, coagulation necrosis, fat necrosis, and parenchymal cell necrosis. Cellular injury and death result in the liberation of bradykinin peptides, vasoactive substances, and histamine that can produce vasodilation, increased vascular permeability, and edema with profound effects on many organs. The systemic inflammatory response syndrome and acute respiratory distress syndrome, as well as multiorgan failure, may occur as a result of this cascade of local and distant effects.

VII-117. The answer is C. *(Chap. 341)* A low-fat solid diet can be administered to subjects with mild acute pancreatitis after the abdominal pain has resolved. Persistent inflammatory changes in the pancreas may remain for weeks to months after an episode of acute pancreatitis. Similarly, there may be prolonged elevation of amylase and lipase. In this regard, persistent changes on CT or persistent pancreatic enzyme elevation should not discourage clinicians from feeding hungry patients with acute pancreatitis. Although there had been prior concern that feeding patients with pancreatitis may exacerbate pancreatic inflammation, this has not been demonstrated. Enteral feeding maintains gut barrier integrity, limits bacterial translocation, is less expensive, and has fewer complications than total parenteral nutrition. The choice of gastric versus nasojejunal enteral feeding is currently under investigation.

VII-118. The answer is D. *(Chap. 341)* Chronic pancreatitis is a common disorder in any patient population with relapsing acute pancreatitis, especially patients with alcohol dependence, pancreas divisum, and cystic fibrosis. The disorder is notable for both endocrine and exocrine dysfunction of the pancreas. Often, diabetes ensues as a result of loss of islet cell function; although insulin-dependent, it is generally not as prone to diabetic ketoacidosis or coma as are other forms of diabetes mellitus. Because pancreatic enzymes are essential to fat digestion, their absence leads to fat malabsorption and steatorrhea. In addition, the fat-soluble vitamins (A, D, E, and K) are not absorbed. Vitamin A deficiency can lead to neuropathy. Vitamin B_{12}, or cobalamin, is often deficient. This deficiency is hypothesized to be due to excessive binding of cobalamin by cobalamin-binding proteins other than intrinsic factors that are normally digested by pancreatic enzymes. Replacement of pancreatic enzymes orally with meals will correct the vitamin deficiencies and steatorrhea. The incidence of pancreatic adenocarcinoma is increased in patients with chronic pancreatitis, with a 20-year cumulative incidence of 4%. Chronic abdominal pain is nearly ubiquitous in this disorder, and narcotic dependence is common. Niacin is a water-soluble vitamin, and absorption is not affected by pancreatic exocrine dysfunction.

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SECTION VIII

Rheumatology and Immunology

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

VIII-1. A 55-year-old woman who was previously incarcerated has an area of induration that measures 15 mm 72 hours after a skin test with tuberculin purified protein derivative (PPD). A positive PPD skin test for *Mycobacterium tuberculosis* represents which type of immune reaction?

A. Cytotoxic reaction of antibody
B. Delayed-type hypersensitivity reaction
C. Immediate-type hypersensitivity reaction
D. Immune complex formation

VIII-2. All of the following are key features of the innate immune system EXCEPT:

A. Exclusively a feature of vertebrate animals
B. Important cells include macrophages and natural killer lymphocytes
C. Nonrecognition of benign foreign molecules or microbes
D. Recognition by germline-encoded host molecules
E. Recognition of key microbe virulence factors but no recognition of self-molecules

VIII-3. A 29-year-old man with episodic abdominal pain and stress-induced edema of the lips, tongue, and occasionally larynx is likely to have low functional or absolute levels of which of the following proteins?

A. C1 esterase inhibitor
B. C5A (complement cascade)
C. Cyclooxygenase
D. IgE
E. T-cell receptor, α chain

VIII-4. Which of the following diseases has a strong genetic association with a particular class I major histocompatibility complex alleles?

A. Ankylosing spondylitis
B. Celiac disease
C. Huntington disease
C. Rheumatoid arthritis
D. Type 1 diabetes

VIII-5. Which of the following statements best describes the function of proteins encoded by the human major histocompatibility complex I and II genes?

A. Activation of the complement system
B. Binding to cell surface receptors on granulocytes and macrophages to initiate phagocytosis
C. Nonspecific binding of antigen for presentation to T cells
D. Specific antigen binding in response to B-cell activation to promote neutralization and precipitation

VIII-6. All of the following statements regarding primary immunodeficiency disorders are true EXCEPT:

A. Infections of the upper or lower respiratory tract suggest a defective antibody response.
B. Most are diagnosed by the presence of recurrent or unusually severe infections.
C. Recurrent infections due to *Candida* species suggest impaired T-cell immunity.
D. They are typically genetic diseases with Mendelian inheritance.
E. While most aspects of the immune system may be involved, innate immunity is not affected by these disorders.

VIII-7. A 19-year-old college freshman comes to the university clinic complaining of tender, painful skin lesions in his axilla (Figure VIII-7). He reports that he has had similar episodes throughout his life for which he receives antibiotics. He has a lab printout from his last episode that reports a positive culture for *Serratia marcescens*. All of the following statements regarding this patient and his likely diagnosis are true EXCEPT:

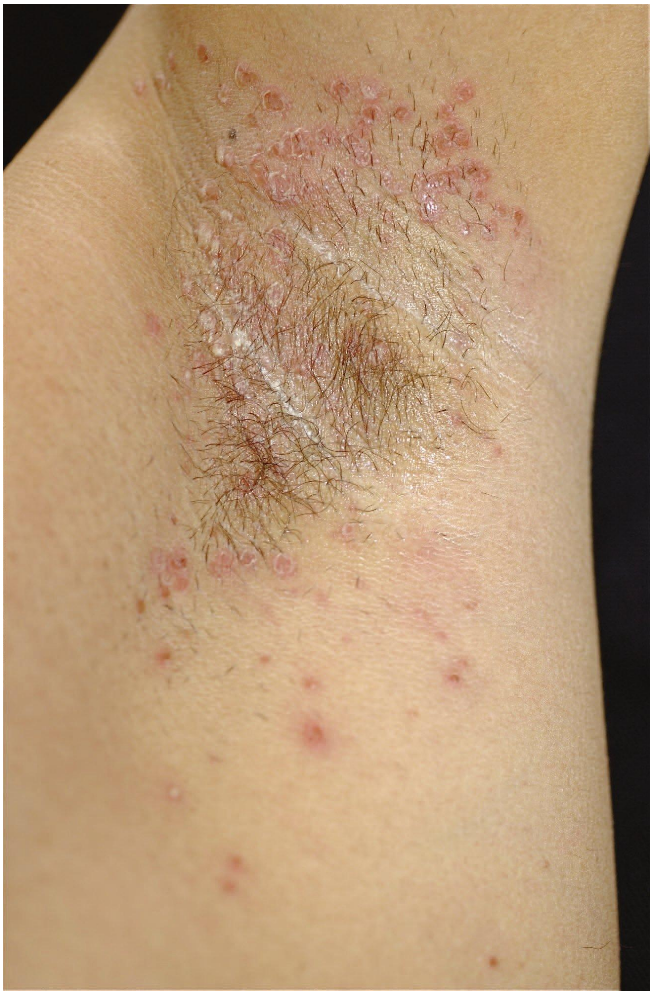


FIGURE VIII-7 Reproduced with permission from Wolff K et al: *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology*, 8th ed. New York: McGraw Hill, 2017.

A. Human stem cell transplantation is curative.
B. Infections with catalase-negative organisms are typical.
C. Prophylactic use of trimethoprim/sulfamethoxazole is effective in reducing risk of bacterial infections.
D. The disease is caused by defective production of reactive oxygen species in phagolysosomes.
E. The disease is most likely transmitted by X-linked recessive inheritance.

VIII-8. A 35-year-old woman from Virginia presents to your clinic with worsening sneezing, rhinorrhea, and nasal itching, which has recurred yearly since she was an adolescent starting in March and increasing during April and May. Based on this history she has an elevated risk of having all of the following additional conditions EXCEPT:

A. Asthma
B. Chronic bilateral sinusitis
C. Food allergies
D. Psoriasis
E. Urticaria

VIII-9. A 28-year-old woman seeks evaluation from her primary care doctor for recurrent episodes of hives and states that she is "allergic to cold weather." She reports that for more than 10 years she would develop areas of hives when exposed to cold temperatures, usually on her arms and legs. She has never sought evaluation previously and states that, over the last several years, the occurrence of the hives has become more frequent. Other than cold exposure, she can identify no other triggers for development of hives. She has no history of asthma or atopy. She denies food intolerance. Her only medication is oral contraceptive pills, which she has taken for 5 years. She lives in a single-family home that was built 2 years ago. On examination, she develops a linear wheal after being stroked along her forearm with a tongue depressor. On placing her hand in cold water, her hand becomes red and swollen. In addition, there are several areas with a wheal and flare reaction on the arm above the area of cold exposure. What is the next step in the management of this patient?

A. Assess for the presence of antithyroglobulin and antimicrosomal antibodies
B. Check C1 inhibitor levels
C. Discontinue the oral contraceptive pills
D. Treat with cetirizine 10 mg daily
E. Treat with cyproheptadine 8 mg daily

VIII-10. A 45-year-old man from Arkansas with a history of hypertension that is treated with lisinopril and colorectal cancer presents to your clinic for a follow-up appointment after a recent emergency room visit. He tells you he was recently diagnosed with an episode of anaphylaxis. He presented to an emergency room with laryngeal edema and diffuse urticaria and was treated successfully with epinephrine. On further history, he tells you more about his recent diagnosis of colorectal cancer for which he has received several doses of cetuximab. He was also sick with shortness of breath and cough 2 weeks prior to the anaphylactic episode. He was evaluated with a CT of the chest with IV contrast, diagnosed with pneumonia, and treated with ceftriaxone. Immediately before his episode of anaphylaxis, he had been enjoying a steak dinner for his wife's birthday. What is the antigen for the IgE antibodies that most likely caused his anaphylactic reaction?

A. Alpha-1,3-galactose (alpha-gal)
B. Ceftriaxone
C. Iodinated contrast
D. Lisinopril

VIII-11. You are working in the emergency department when a 3-year-old boy arrives by ambulance. He was eating tonight when he suddenly started wheezing, coughing, and then became progressively less responsive. His parents are certain he did not aspirate. On arrival, his blood pressure is low, and he is working hard to breathe. You auscultate tight wheezes bilaterally. You accurately diagnose him with anaphylaxis and initiate appropriate therapy. Which of the following statements regarding anaphylaxis is true?

A. An atopic history is a risk factor for anaphylaxis to penicillin therapy.
B. Onset of anaphylaxis is most often 1–2 hours after antigen exposure.
C. IV glucocorticoids are effective for acute anaphylaxis.
D. Older age is associated with improved outcomes in anaphylaxis.
E. The failure to use epinephrine within the first 20 minutes of symptoms is a risk factor for death due to anaphylaxis.

VIII-12. A 60-year-old man presents to the clinic with intermittent flushing, diarrhea, headaches, and a new skin rash of several months' duration. He has noticed that his symptoms of diarrhea and flushing tend to worsen if he takes ibuprofen to treat his headaches. On examination, he has a palpable spleen and cervical lymphadenopathy. Serum tryptase is elevated at 35 ng/mL. His skin rash is shown in Figure VIII-12. A diagnostic skin biopsy is performed. What histological findings are most likely to be noted on the skin biopsy?

A. Interface dermatitis
B. Multifocal dense infiltrates of mast cells
C. Neutrophilic dermal infiltrate
D. Noncaseating granulomas
E. Spongiotic changes in the epidermis

VIII-13. A 25-year-old man is admitted to the intensive care unit with hypoxemia. His partner tells the intensive care team that he has been coughing up blood for the last 2 days in increasing amounts. On laboratory studies his creatinine is markedly elevated. He is ultimately diagnosed with Goodpasture syndrome. What is the immune mechanism leading to organ damage in Goodpasture syndrome?

A. Antibody-dependent cellular cytotoxicity
B. Complement-activating autoantibody
C. Inactivating autoantibody
D. Stimulating autoantibody
E. T-cell–mediated cellular cytotoxicity

VIII-14. Rheumatic fever develops due to an autoimmune process. Which of the following mechanisms of autoimmunity is primarily responsible for the development of rheumatic fever?

A. Endocrine abnormalities
B. Increased B-cell function
C. Intrinsic cytokine imbalance
D. Increased T-cell help due to cytokine stimulation
E. Molecular mimicry

VIII-15. A 60-year-old Caucasian man with a history of psoriasis presents to the clinic for a follow-up appointment. He has been treated with infliximab (a tumor necrosis factor inhibitor) for about a year. Since his last infusion of infliximab, he has been experiencing aching in his muscles and joints and a new facial rash. On examination you note a raised erythematous malar rash, but there is no synovitis in any joints and there is no weakness on neurologic examination. Laboratory testing shows a positive anti-nuclear antibody at a titer of 1:320. Which specific autoantibody is most likely to be present?

A. Anti-β-2-glycoprotein
B. Anti-cyclic citrullinated protein antibodies
C. Anti-dsDNA antibodies
D. Anti-histone antibodies
E. Anti-thyroid peroxidase antibodies

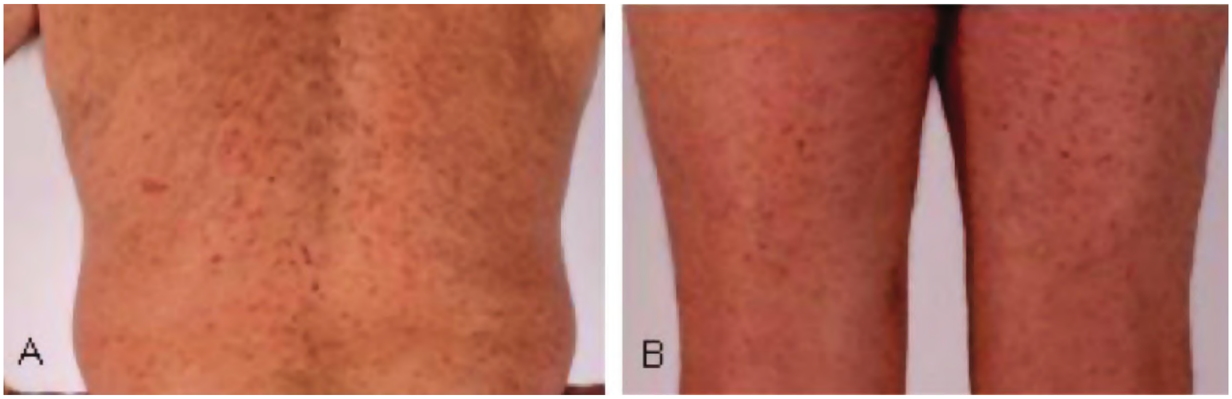


FIGURE VIII-12 Reproduced with permission from Lichtman MA et al: *Lichtman's Atlas of Hematology 2016*. New York: McGraw Hill, 2017.

VIII-16. All of the following are predisposing factors for systemic lupus erythematosus EXCEPT:

A. C1 esterase inhibitor deficiency
B. Female sex
C. HLA-DR alleles
D. Smoking
E. Ultraviolet light

VIII-17. A 32-year-old woman with long-standing diagnosis of systemic lupus erythematosus is evaluated by her rheumatologist as routine follow-up. A new cardiac murmur is heard, and an echocardiogram is ordered. She is feeling well and has no fevers, weight loss, or pre-existing cardiac disease. A vegetation on the mitral valve is demonstrated. Which of the following statements is true?

A. Blood cultures are unlikely to be positive.
B. Glucocorticoid therapy has been proven to lead to improvement in this condition.
C. Pericarditis is frequently present concomitantly.
D. The lesion has a low risk of embolization.
E. The patient has been surreptitiously using injection drugs.

VIII-18. A 45-year-old African American woman with systemic lupus erythematosus (SLE) presents to the emergency department with complaints of headache and fatigue. Her prior manifestations of SLE have been arthralgias, hemolytic anemia, malar rash, and mouth ulcers, and she is known to have high titers of antibodies to double-stranded DNA. She currently is taking prednisone, 5 mg daily, and hydroxychloroquine, 200 mg daily. On presentation, she is found to have a blood pressure of 190/110 with a heart rate of 98 beats/min. A urinalysis shows 25 red blood cells (RBCs) per high-powered field with 2+ proteinuria. No RBC casts are identified. Her blood urea nitrogen is 88 mg/dL, and creatinine is 2.6 mg/dL (baseline 0.8 mg/dL). She has not previously had renal disease related to SLE and is not taking nonsteroidal anti-inflammatory drugs. She denies any recent illness, decreased oral intake, or diarrhea. What is the most appropriate next step in the management of this patient?

A. Initiate cyclophosphamide, 500 mg/m^2 body surface area IV, and plan to repeat monthly for 3–6 months
B. Initiate hemodialysis
C. Initiate high-dose steroid therapy (IV methylprednisolone, 1000 mg daily for three doses, followed by oral prednisone, 1 mg/kg daily) and mycophenolate mofetil, 2 g daily
D. Initiate plasmapheresis
E. Withhold all therapy until renal biopsy is performed

VIII-19. All of the following statements regarding antiphospholipid antibodies are true EXCEPT:

A. Antiphospholipid antibodies are generally directed against negatively charged phospholipids including cardiolipin, phosphocholine, and phosphatidylserine.
B. Patients who are positive for the lupus anticoagulant will have an elevated activated partial thromboplastin time in vitro.
C. Patients with antiphospholipid antibodies may test false positive for syphilis.
D. The majority of patients with systemic lupus erythematosus and antiphospholipid antibodies develop clinical manifestations of antiphospholipid syndrome.

VIII-20. A 27-year-old woman is admitted to the intensive care unit after recent delivery of a full-term infant 3 days prior. The patient was found to have right hemiparesis and a blue left hand. Physical examination is also notable for livedo reticularis. Her laboratories were notable for a white blood cell count of 10.2/μL, hematocrit of 35%, and platelet count of 13,000/μL. Her blood urea nitrogen is 36 mg/dL, and her creatinine is 2.3 mg/dL. Although this pregnancy was uneventful, the three prior pregnancies resulted in early losses. A peripheral smear shows no evidence of schistocytes. Which of the following laboratory studies will best confirm the underlying etiology of her presentation?

A. Anticardiolipin antibody panel
B. Antinuclear antibody
C. Doppler examination of her left arm arterial tree
D. Echocardiography
E. MRI of her brain

VIII-21. A 28-year-old woman comes to the emergency department complaining of 1 day of worsening right leg pain and swelling. She drove in a car 8 hours back from a hiking trip 2 days ago and then noticed some pain in the leg. At first she thought it was due to exertion, but it has worsened over the day. Her only past medical history is related to difficulty getting pregnant, with two prior spontaneous abortions. Her physical examination is notable for normal vital signs and heart and lung examination. Her right leg is swollen from the mid-thigh down and is tender. Doppler studies demonstrate a large deep venous thrombosis in the femoral and iliac veins extending into the pelvis. Laboratory studies on admission prior to therapy show normal electrolytes, normal white blood cell and platelet counts, normal prothrombin time, and an activated partial thromboplastin time three times the normal value. Her pregnancy test is negative. Low-molecular-weight heparin therapy is initiated in the emergency department. Subsequent therapy should include which of the following?

A. Rituximab 375 mg/m^2 per week for 4 weeks
B. Warfarin with international normalized ratio (INR) goal of 2.0–3.0 for 3 months
C. Warfarin with INR goal of 2.0–3.0 for 12 months
D. Warfarin with INR goal of 2.5–3.5 for life
E. Warfarin with an INR goal of 2.5–3.5 for 12 months followed by daily aspirin for life

VIII-22. When compared with patients with rheumatoid arthritis (RA) who do not have anti-cyclic citrullinated protein (CCP) antibodies, patients with RA who have anti-CCP antibodies:

A. Are less likely to develop extra-articular manifestations of RA (e.g., vasculitis)
B. Are less likely to have a history of smoking
C. Develop fewer subchondral bone erosions on imaging over their disease course
D. Have a higher prevalence of shared epitope (HLA-DRB1) risk alleles
E. Have lower scores for physical disability

VIII-23. A 65-year-old woman with a 10-year history of untreated rheumatoid arthritis presents to your clinic with worsening joint pain and malaise over the last 6 months. On examination of her joints, she has swan neck deformities and ulnar deviation. Her skin examination demonstrates rheumatoid nodules in the olecranon bursa bilaterally. On abdominal examination, she has splenomegaly. Laboratory studies show neutropenia, elevated C-reactive protein, and anemia. She is diagnosed with Felty syndrome. What type of hematologic malignancy or lymphoproliferative disorder may present similarly to Felty syndrome in patients with rheumatoid arthritis?

A. Acute myeloid leukemia
B. Chronic lymphocytic leukemia
C. Essential thrombocytosis
D. Polycythemia vera
E. T-cell large granular lymphocyte leukemia

VIII-24. Patients with rheumatoid arthritis are at higher risk for all of the following health conditions than the general population EXCEPT:

A. Colorectal cancer
B. Coronary artery disease
C. Hypoandrogenism
D. Lymphoma
E. Osteoporosis

VIII-25. Which of the following is the most frequent site of joint involvement in established rheumatoid arthritis?

A. Distal interphalangeal joint
B. Hip
C. Knee
D. Spine
E. Wrist

VIII-26. In patients with established rheumatoid arthritis, all of the following pulmonary radiographic findings may be explained by their rheumatologic condition EXCEPT:

A. Bilateral interstitial infiltrates
B. Bronchiectasis
C. Lobar infiltrate
D. Solitary pulmonary nodule
E. Unilateral pleural effusion

VIII-27. Which of the following is the earliest plain radiographic finding of rheumatoid arthritis?

A. Juxta-articular osteopenia
B. No abnormality
C. Soft tissue swelling
D. Subchondral erosions
E. Symmetric joint space loss

VIII-28. All of the following agents have been shown to have disease-modifying antirheumatic drug efficacy in patients with rheumatoid arthritis EXCEPT:

A. Infliximab
B. Leflunomide
C. Methotrexate
D. Naproxen
E. Rituximab

VIII-29. Which of the following findings is the most common clinical presentation of acute rheumatic fever?

A. Carditis
B. Chorea
C. Erythema marginatum
D. Polyarthritis
E. Subcutaneous nodules

VIII-30. A 19-year-old recent immigrant from Ethiopia comes to your clinic to establish primary care. She currently feels well. Her past medical history is notable for a recent admission to the hospital for new-onset atrial fibrillation. As a child in Ethiopia, she developed an illness that caused uncontrolled flailing of her limbs and tongue lasting approximately 1 month. She also has had three episodes of migratory large-joint arthritis during her adolescence that resolved with pills that she received from the pharmacy. She is currently taking metoprolol and warfarin and has no known drug allergies. Physical examination reveals an irregularly irregular heart beat with normal blood pressure. Her point of maximal impulse is most prominent at the midclavicular line and is normal in size. An early diastolic rumble and 3/6 holosystolic murmur are heard at the apex. A soft early diastolic murmur is also heard at the left third intercostal space. You refer her to a cardiologist for evaluation of valve replacement and echocardiography. What other intervention might you consider at this time?

A. Daily aspirin
B. Daily doxycycline
C. Low-dose corticosteroids
D. Monthly penicillin G injections
E. Penicillin G injections as needed for all sore throats

VIII-31. Most of the manifestations of acute rheumatic fever present approximately 3 weeks after the precipitating group A streptococcal infection. Which manifestation may present several months after the precipitating infection?

A. Chorea
B. Erythema marginatum
C. Fever
D. Polyarthritis
E. Subcutaneous nodules

VIII-32. A 60-year-old woman with long-standing scleroderma (Raynaud phenomenon, diffuse skin disease, and pulmonary fibrosis) presents to the clinic with new weight loss. She has also been noting increased lower abdominal pain, bloating, and diarrhea recently. She denies any heartburn or dysphagia. She has not had melena or hematochezia. Which of the following mechanisms related to her scleroderma could be contributing to her symptoms?

A. Gastric antral vascular ectasia
B. Gastroesophageal reflux disease
C. Impaired intestinal motility
D. Small bowel bacterial overgrowth
E. C and D

VIII-33. Patients with scleroderma are at higher risk for all of the following complications in the cardiovascular system EXCEPT:

A. Abdominal aortic aneurysm
B. Heart block due to conduction system fibrosis
C. Left ventricular dysfunction
D. Pulmonary arterial hypertension
E. Raynaud phenomenon

VIII-34. A patient with a diagnosis of scleroderma who has diffuse cutaneous involvement presents with malignant hypertension, oliguria, edema, hemolytic anemia, and renal failure. You make a diagnosis of scleroderma renal crisis. Which of the following is the recommended treatment?

A. Captopril
B. Carvedilol
C. Clonidine
D. Diltiazem
E. Nitroprusside

VIII-35. Which of the following conditions is nearly twice as common in patients with diffuse cutaneous systemic sclerosis than in limited cutaneous systemic sclerosis?

A. Esophageal involvement
B. Pulmonary arterial hypertension
C. Pulmonary fibrosis
D. Raynaud phenomenon
E. Skin involvement

VIII-36. A 22-year-old man with a history of injection drug use presents to the clinic with a new complaint of dry mouth. He denies any eye dryness, photosensitivity, or foreign body sensation in the eye. He has also experienced weight loss and night sweats. Physical examination shows parotid gland swelling bilaterally and decreased salivary pooling, but no rashes, joint swelling, or other findings. Laboratory testing is negative for anti-nuclear antibodies, Ro/SS-A antibodies, and La/SS-B antibodies. Chest radiograph shows no infiltrates or lymphadenopathy. What is the most likely diagnosis?

A. HIV infection
B. IgG4-related disease
C. Primary Sjögren syndrome
D. Rheumatoid arthritis with secondary Sjögren syndrome
E. Sarcoidosis

VIII-37. A 57-year-old woman with depression and chronic migraine headaches reports several years of dry mouth and dry eyes. Her primary complaint is that she can no longer eat her favorite crackers, although she does report photosensitivity and eye burning on further questioning. She has no other associated symptoms. Examination shows dry, erythematous, sticky oral mucosa. All of the following tests are likely to be positive in this patient EXCEPT:

A. La/SS-B antibody
B. Ro/SS-A antibody
C. Schirmer I test
D. Scl-70 antibody
E. Sialometry

VIII-38. A patient with primary Sjögren syndrome that was diagnosed 6 years ago and treated with tear replacement for symptomatic relief notes continued parotid swelling for the last 3 months. She has also noted enlarging posterior cervical lymph nodes. Evaluation shows leukopenia and low C4 complement levels. What is the most likely diagnosis?

A. Amyloidosis
B. Chronic pancreatitis
C. HIV infection
D. Lymphoma
E. Secondary Sjögren syndrome

VIII-39. Which of the following is the most common extraglandular manifestation of primary Sjögren syndrome?

A. Arthralgias/arthritis
B. Lymphoma
C. Peripheral neuropathy
D. Raynaud phenomenon
E. Vasculitis

VIII-40. All of the following medications are effective in treating both psoriatic arthritis and the skin disease of psoriasis EXCEPT:

A. Adalimumab
B. Infliximab
C. Rituximab
D. Secukinumab
E. Ustekinumab

VIII-41. A 30-year-old woman presents to an internal medicine clinic for evaluation of joint pain and swelling of about 2 years duration accompanied by morning stiffness. She denies any back or neck pain. Symptoms have primarily affected her lower extremities. She notes intermittent swelling in her Achilles tendons, ankles, and knees. She denies any psoriasis or family history of skin disease. She denies any gastrointestinal symptoms or preceding infectious episodes. On physical examination she has right-sided Achilles enthesitis, left ankle synovitis, and dactylitis of the third and fourth fingers of her right hand. Imaging of her sacroiliac joints with MRI shows no erosions or bone marrow edema. Laboratory testing shows an elevated C-reactive protein, negative rheumatoid factor, and negative anti-cyclic citrullinated protein antibodies. Which of the following is the most likely diagnosis?

A. Ankylosing spondylitis
B. Peripheral spondyloarthritis
C. Psoriatic arthritis
D. Reactive arthritis
E. Rheumatoid arthritis

VIII-42. Which of the following clinical manifestations can be seen in the syndrome of synovitis, acne, pustulosis, hyperostosis, and osteitis?

A. Acromegaly
B. Hidradenitis suppurativa
C. Plaque psoriasis
D. Sternoclavicular osteomyelitis
E. B and D

VIII-43. Histocompatibility antigen human leukocyte antigen-B27 is present in what percentage of North American patients with ankylosing spondylitis?

A. 10%
B. 30%
C. 50%
D. 80%
E. 100%

VIII-44. Which of the following is the most common extra-articular manifestation of ankylosing spondylitis?

A. Anterior uveitis
B. Aortic insufficiency
C. Inflammatory bower disease
D. Pulmonary fibrosis
E. Third-degree heart block

VIII-45. A 27-year-old man is seen at his primary care physician's office for evaluation of painful arthritis involving the right knee associated with diffuse bilateral finger swelling. He is otherwise healthy but does recall a severe bout of diarrheal illness about 3–4 weeks prior that spontaneously resolved. He works as a recreation supervisor at a daycare center and said many of the children had a similar diarrheal illness. He takes no medications and reports rare marijuana use. On review of systems, he reports painful urination. Examination shows inflammatory arthritis of the right knee, dactylitis, and normal genitourinary examination. He is diagnosed with reactive arthritis. Which of the following was the most likely etiologic agent of his diarrhea?

A. *Campylobacter jejuni*
B. *Clostridium difficile*
C. *Escherichia coli*
D. *Helicobacter pylori*
E. *Shigella flexneri*

VIII-46. Which of the following definitions best fits the term enthesitis?

A. A palpable vibratory or crackling sensation elicited with joint motion
B. Alteration of joint alignment so that articulating surfaces incompletely approximate each other
C. Inflammation at the site of tendinous or ligamentous insertion into bone
D. Inflammation of the periarticular membrane lining the joint capsule
E. Inflammation of a saclike cavity near a joint that decreases friction

VIII-47. All of the following help distinguish psoriatic arthritis from other joint disorders EXCEPT:

A. Dactylitis
B. Enthesitis
C. Nail pitting
D. Presence of diarrhea
E. Shortening of digits

VIII-48. Which cardiac valvular lesion is most common in patients with ankylosing spondylitis?

A. Aortic regurgitation
B. Mitral regurgitation
C. Mitral stenosis
D. Pulmonic stenosis
E. Tricuspid regurgitation

VIII-49. A 55-year-old man presents to the emergency department with weight loss, fever, testicular pain, and a new rash on his legs. On physical examination, he has abdominal tenderness and raised nonblanching erythematous lesions on his legs. Laboratory studies show an elevated erythrocyte sedimentation rate and C-reactive protein as well as a positive hepatitis B surface antigen. He undergoes a surgical skin biopsy. The biopsy is most likely to show:

A. Fibrinoid necrosis of small- and medium-sized arteries
B. Interface dermatitis
C. Leukocytoclastic vasculitis with IgA deposition on immunofluorescence
D. Noncaseating granulomas
E. Septal panniculitis

VIII-50. All of the following arteries are commonly affected in Takayasu arteritis EXCEPT:

A. Abdominal aorta
B. Cerebral arteries
C. Common carotid artery
D. Renal arteries
E. Subclavian artery

VIII-51. A 40-year-old male presents to the emergency department with 2 days of low-volume hemoptysis. He reports that he has been coughing up 2–5 tablespoons of blood each day. He does report mild chest pain, low-grade fevers, and weight loss. In addition, he has had about 1 year of severe upper respiratory symptoms including frequent epistaxis and purulent discharge treated with several courses of antibiotics. Aside from mild hyperlipidemia, he is otherwise healthy. His only medications are daily aspirin and lovastatin. On physical examination he has a saddle nose deformity. His vital signs are normal and his lungs are clear. A CT of the chest shows multiple 1- to 2-cm cavitating nodules, and urinalysis shows red blood cells. Which of the following tests offers the highest diagnostic yield to make the appropriate diagnosis?

A. Deep skin biopsy
B. Percutaneous kidney biopsy
C. Pulmonary angiogram
D. Surgical lung biopsy
E. Upper airway biopsy

VIII-52. An 84-year-old woman is seen by her primary care physician for evaluation of severe headaches. She noted these several weeks ago, and they have been getting worse. Although she has not had any visual aura, she is concerned that she has been intermittently losing vision in her left eye for the last few days. She denies new weakness or numbness, but she does report jaw pain with eating. Her past medical history includes coronary artery disease requiring a bypass grafting 10 years prior, diabetes mellitus, hyperlipidemia, and mild depression. Full review of symptoms is notable for night sweats and mild low back pain particularly prominent in the morning. Which of the following is the next most appropriate step?

A. Aspirin 975 mg orally daily
B. Measurement of erythrocyte sedimentation rate
C. Immediate initiation of glucocorticoid treatment
D. Referral for temporal artery biopsy
E. Referral for ultrasound of temporal artery

VIII-53. A 54-year-old man is evaluated for cutaneous vasculitis and peripheral nephropathy. Because of concomitant renal dysfunction, he undergoes kidney biopsy that shows glomerulonephritis. Cryoglobulins are demonstrated in the peripheral blood. Which of the following laboratory studies should be sent to determine the etiology?

A. Hepatitis B surface antigen
B. Antineutrophil cytoplasmic antibody
C. Hepatitis C polymerase chain reaction
D. HIV antibody
E. Rheumatoid factor

VIII-54. An 18-year-old man is admitted to the hospital with acute onset of crushing substernal chest pain that began abruptly 30 minutes ago. He reports the pain radiating to his neck and right arm. He has otherwise been in good health. He currently plays trumpet in his high school marching band but does not participate regularly in aerobic activities. On physical examination, he is diaphoretic and tachypneic. His blood pressure is 100/48 and heart rate is 110 beats/min. His cardiovascular examination has a regular rhythm but is tachycardic. A 2/6 holosystolic murmur is heard best at the apex and radiates to the axilla. His lungs have bilateral rales at the bases. The electrocardiogram demonstrates 4 mm of ST elevation in the anterior leads. On further questioning regarding his past medical history, he recalls having been told that he was hospitalized for some problem with his heart when he was 2 years old. His mother, who accompanies him, reports that he received aspirin and γ-globulin as treatment. Since that time, he has required intermittent follow-up with echocardiography. What is the most likely cause of this patient's acute coronary syndrome?

A. Dissection of the aortic root and left coronary ostia
B. Presence of a myocardial bridge overlying the left anterior descending artery
C. Thrombosis of a coronary artery aneurysm
D. Vasospasm following cocaine ingestion
E. Vasculitis involving the left anterior descending artery

VIII-55. You are seeing in follow-up a 46-year-old man who, 6 months ago, presented to the hospital acutely with hemoptysis, diffuse nodular pulmonary infiltrates, and glomerulonephritis. Workup revealed a positive serologic study for antibodies against cytoplasmic antineutrophil cytoplasmic antibodies (ANCA), and he was eventually diagnosed with granulomatosis with polyangiitis. Treatment was initiated with high-dose glucocorticoids and daily cyclophosphamide with excellent clinical response. You are ready today to have the patient transition from induction therapy with cyclophosphamide to maintenance therapy with azathioprine. What blood test should you check before starting azathioprine?

A. ANCA titers
B. Cryoglobulins
C. CYP3A4 genotyping
D. Glucose-6-phosphate dehydrogenase enzyme levels
E. Thiopurine methyltransferase enzyme activity

VIII-56. Lung biopsy has the greatest diagnostic yield in which of the following vasculitic syndromes?

A. Cryoglobulinemic vasculitis
B. Cutaneous vasculitis
C. Granulomatosis with polyangiitis (Wegener)
D. IgA vasculitis (Henoch-Schönlein)
E. Polyarteritis nodosa

VIII-57. All of the following conditions occur in association with Behçet syndrome EXCEPT:

A. Arthritis
B. Deep venous thrombosis
C. Folliculitis
D. Genital ulcers
E. Scleritis

VIII-58. Which of the following is required for the diagnosis of Behçet syndrome?

A. Large vessel vasculitis
B. Pathergy test
C. Recurrent oral ulceration
D. Recurrent genital ulceration
E. Uveitis

VIII-59. A 25-year-old woman presents with a complaint of painful mouth ulcerations. She describes these lesions as shallow ulcers that last for 1 or 2 weeks. The ulcers have been appearing for the last 6 months. For the last 2 days, the patient has had a painful red eye. She has had no genital ulcerations, arthritis, skin rashes, or photosensitivity. On physical examination, the patient appears well developed and in no distress. She has a temperature of 37.6°C (99.7°F), heart rate of 86 beats/min, blood pressure of 126/72, and respiratory rate of 16 breaths/min. Examination of the oral mucosa reveals two shallow ulcers with a yellow base on the buccal mucosa. The ophthalmologic examination is consistent with anterior uveitis. The cardiopulmonary examination is normal. She has no arthritis, but medially on the right thigh, there is a palpable cord in the saphenous vein. Laboratory studies reveal an erythrocyte sedimentation rate of 68 seconds. White blood cell count is 10,230/μL with a differential of 68% polymorphonuclear cells, 28% lymphocytes, and 4% monocytes. The anti-nuclear antibody and anti-dsDNA antibody are negative, and C3 is 89 mg/dL and C4 is 24 mg/dL. What is the most likely diagnosis?

A. Behçet syndrome
B. Bullous pemphigoid
C. Discoid lupus erythematosus
D. Sjögren syndrome
E. Systemic lupus erythematosus

VIII-60. A 58-year-old man presents to the clinic for a routine follow-up visit. He notes he has been dropping things more frequently and is having trouble rising from a seated position. He also notes some trouble swallowing and needing to swallow multiple times for one bite of food. On physical examination he has 4/5 strength in his knee extensors, 3/5 strength in his finger flexors, and atrophy in the medial thighs and forearms. On laboratory studies, his creatinine kinase is two times the upper limit of normal. You decide to pursue a muscle biopsy. What findings are likely to be noted on the muscle biopsy by light microscopy?

A. Multifocal necrotic and regenerating muscle fibers with a paucity of inflammation
B. Perifascicular muscle atrophy
C. Perivascular inflammatory cell infiltrate with no endomysial inflammation
D. Rimmed vacuoles and inclusions
E. Type 2 muscle fiber atrophy

VIII-61. All of the following therapeutic agents are used in the treatment of polymyositis EXCEPT:

A. Azathioprine
B. Mycophenolate Mofetil
C. Prednisone
D. Rituximab
E. Secukinumab

VIII-62. A 64-year-old woman is evaluated for weakness. She has had several weeks of difficulty brushing her teeth and combing her hair. She has also noted a rash on her face. Examination is notable for a heliotrope rash and proximal muscle weakness. Serum creatinine kinase is elevated, and she is diagnosed with dermatomyositis. After evaluation by a rheumatologist, she is found to have anti-Jo-1 antibodies. She is also likely to have which of the following additional findings?

A. Ankylosing spondylitis
B. Inflammatory bowel disease
C. Interstitial lung disease
D. Primary biliary cirrhosis
E. Psoriasis

VIII-63. A 63-year-old woman is evaluated for a rash on her eyes and fatigue for 1 month. She reports difficulty with arm and leg strength and constant fatigue, but no fevers or sweats. She also has noted that she has a red discoloration around her eyes. She has hypothyroidism but is otherwise well. On examination, she has a heliotrope rash and proximal muscle weakness. A diagnosis of dermatomyositis is made after demonstration of elevated serum creatinine kinase and confirmatory electromyograms. Which of the following studies should be performed as well to look for associated conditions?

A. Mammogram
B. Serum anti-nuclear antibody measurement
C. Stool examination for ova and parasites
D. Thyroid-stimulating immunoglobulins
E. Titers of antibodies to varicella zoster

VIII-64. You are seeing your long-term patient in the clinic. He has a history of coronary artery disease, with a lateral myocardial infarction 1 year ago. At that time, he was started on simvastatin, aspirin, metoprolol, and lisinopril. About 2 months ago, he started noting thigh and shoulder soreness. One month after onset, his muscle pain had increased and he was noticing weakness. His creatinine kinase (CK) was elevated to eight times the upper limit of normal. His simvastatin was discontinued 3 weeks ago. Today, he reports that his pain has continued and, if anything, is worse than a month ago. His CK is 12 times the upper limit of normal. What is the next best test to establish a diagnosis?

A. Antibody against 3-hydroxy-3-methylglutaryl–coenzyme A reductase
B. Anti-nuclear antibody
C. Anti-Jo-1 antibody
D. Antibody against signal recognition particle
E. Aldolase levels

VIII-65. Which of the following disorders is associated with relapsing polychondritis?

A. Giant cell arteritis
B. Granulomatosis with polyangiitis (formerly Wegener disease)
C. Rheumatoid arthritis
D. Psoriasis
E. B and C

VIII-66. A 47-year-old man is evaluated for 1 year of recurrent episodes of bilateral ear swelling. The ear is painful during these events, and the right ear has become floppy. He is otherwise healthy and reports no illicit habits. He works in an office, and his only sport is tennis. On examination, the left ear has a beefy red color and the pinna is tender and swollen; the earlobe appears minimally swollen but is neither red nor tender. Which of the following is the most likely explanation for this finding?

A. Behçet syndrome
B. Cogan syndrome
C. Hemoglobinopathy
D. Recurrent trauma
E. Relapsing polychondritis

VIII-67. Which of the following cardiovascular conditions can occur in sarcoidosis as a result of granulomatous infiltration?

A. Abdominal aortic aneurysm
B. Coronary artery disease
C. Decreased ejection fraction
D. Ventricular arrhythmia
E. C and D

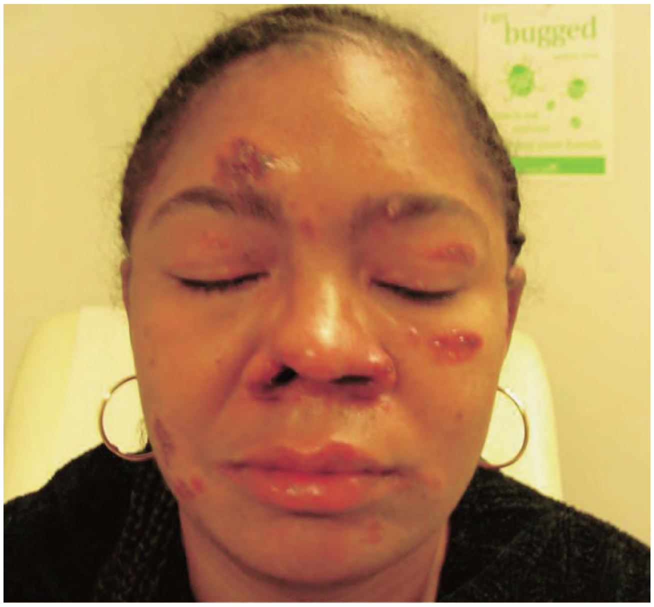


FIGURE VIII-68

VIII-68. A 40-year-old African American woman presents to the clinic with a facial rash. The rash has lasted for several months and is raised and erythematous (Figure VIII-68). She also reports a new dry cough. Chest radiograph shows bilateral hilar lymphadenopathy. What type of skin rash is present?

A. Acne vulgaris
B. Acute cutaneous lupus
C. Erythema nodosum
D. Heliotrope rash
E. Lupus pernio

VIII-69. All of the following have been implicated in the proposed pathogenesis of sarcoidosis EXCEPT:

A. Exposure to mold
B. Genetic susceptibility
C. Immune response to mycobacterial proteins
D. Infection with *Propionibacterium acnes*
E. Malignant expansion of helper T cells

VIII-70. Which of the following statements regarding pulmonary sarcoidosis is true?

A. Lung involvement is the second most common manifestation of sarcoidosis, behind only cutaneous involvement.
B. Obstructive disease is a rare manifestation of pulmonary sarcoidosis.
C. Pulmonary hypertension never responds to therapy in sarcoidosis patients.
D. Pulmonary infiltrates in sarcoidosis tend to be predominantly an upper lobe process.
E. The presence of cough should prompt evaluation for a cause other than pulmonary sarcoidosis.

VIII-71. You are seeing a 55-year-old white man with a history of sarcoidosis. He ran out of prednisone about 2 months prior to seeing you and, except for some constipation, feels well. A metabolic panel reveals a calcium of 12.2 mg/dL (normal up to 10.5 mg/dL). You know that sarcoidosis can be associated with hypercalcemia. Which of the following is the correct mechanism for sarcoidosis-associated hypercalcemia?

A. Direct granulomatous involvement of the axial skeleton causing calcium release from bones
B. Direct stimulation of increased intestinal calcium absorption
C. Increased parathyroid hormone production
D. Increased production of 1,25-dihydroxyvitamin D
E. Increased production of 25-hydroxyvitamin D

VIII-72. All of the following conditions are manifestations of IgG4-related disease EXCEPT:

A. Autoimmune pancreatitis
B. Crescentic glomerulonephritis
C. Lymphoplasmacytic aortitis
D. Orbital pseudotumor
E. Sialadenitis

VIII-73. Your patient is a 34-year-old man who presented to you with unexplained pancreatitis 2 weeks ago. Imaging of his pancreas showed diffuse pancreatic enlargement. He denies any alcohol intake and did not have any gallstones on imaging. Interestingly, on examination, he also has marked lacrimal gland and submandibular gland enlargement. Biopsy of his submandibular gland is pictured in Figure VIII-73. The cells pictured in the figure stain strongly positive for IgG4, CD19, and CD138. Which of the following is the appropriate therapy?

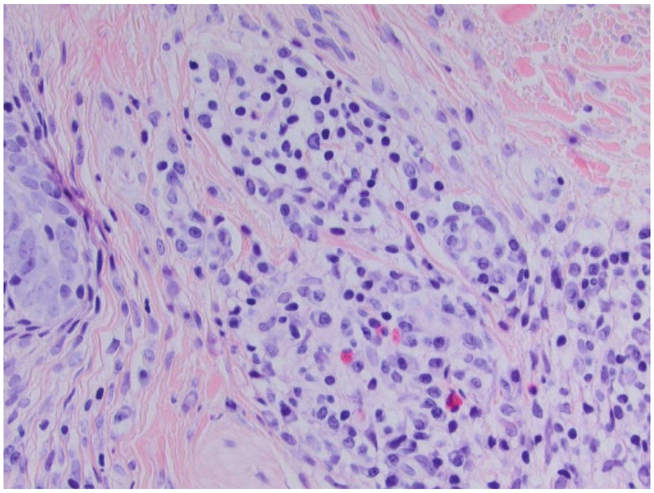


FIGURE VIII-73

A. Thalidomide and dexamethasone
B. Cytomegalovirus immunoglobulin and ganciclovir
C. Systemic chemotherapy
D. Prednisone
E. Anakinra

VIII-74. Which of the following drugs can be used to treat several genetic periodic fever syndromes including Muckle-Wells syndrome, hyperimmunoglobulinemia D with periodic fever syndrome, and tumor necrosis factor-receptor-associated periodic syndrome?

A. Adalimumab
B. Canakinumab
C. Colchicine
D. Lisinopril
E. Rituximab

VIII-75. You are seeing a 19-year-old woman today in consultation for recurrent fevers. She reports several years of fevers, occurring on average every 2–3 months. These episodes are unpredictable, although she thinks they may occur in times of psychological stress. Each febrile episode lasts 2–3 days. She also has recurrent episodes of abdominal pain. Repeated blood cultures have been negative, even during acute febrile episodes. Similarly, abdominal CT scans have shown no obvious etiology for her pain. During one episode, she underwent an exploratory laparotomy, which showed peritoneal adhesions and a sterile neutrophilic peritoneal exudate. She also notes that when she exercises, she develops intense muscle pains that last for days. An extensive serologic search for autoantibodies returned negative, including anti-nuclear antibodies. Which of the following is the most likely diagnosis?

A. Familial Mediterranean fever
B. Lymphoma
C. Relapsing fever
D. Subacute bacterial endocarditis
E. Systemic lupus erythematosus

VIII-76. For the patient described in question VIII-75, which of the following medications would you prescribe to reduce attacks and help prevent the development of systemic amyloidosis?

A. Colchicine
B. Cyclosporine
C. Prednisone
D. Rituximab
E. Vancomycin

VIII-77. In the United States, what percentage of patients over the age of 60 years have symptomatic osteoarthritis of the knee?

A. 1%
B. 5%
C. 12%
D. 30%
E. 43%

VIII-78. Which of the following joints is often spared by osteoarthritis?

A. Cervical spine
B. Distal interphalangeal joint
C. Hip
D. Proximal interphalangeal joint
E. Wrist

VIII-79. Which of the following statements regarding osteoarthritis is true?

A. During the diagnostic workup of a suspected osteoarthritic joint, MRI is warranted to evaluate for any other causes.
B. Loss of cartilage causes pain due to direct stimulation of pain receptors in joint cartilage itself.
C. Osteoarthritis is the second most common cause of arthritis, behind rheumatoid arthritis.
D. Synovial fluid white blood cell count is usually <1000 cells/μL in osteoarthritis.
E. The severity of radiographic changes in osteoarthritis correlates well with symptoms.

VIII-80. You are seeing a 60-year-old obese woman with bilateral knee osteoarthritis. She describes pain most days and limiting pain at least 2 days per week. She has tried activity modification (walking less) without success. All of the following therapies have been shown to be efficacious in treating osteoarthritis symptoms in this patient EXCEPT:

A. Acetaminophen
B. Glucocorticoid intra-articular injections
C. Glucosamine-chondroitin
D. Naproxen
E. Total joint arthroplasty

VIII-81. A 75-year-old woman presents to the clinic with a newly swollen right knee. She denies any fevers, night sweats, or other constitutional symptoms. She does not have any toe, foot, or ankle pain or swelling. She has never had a similar episode previously. She has a history of osteoarthritis and underwent a left total hip arthroplasty 5 years ago. On examination, her right knee is warm with a moderate size effusion and tender to palpation. Laboratory studies show a uric acid level of 5.2 mg/dL (normal). A radiograph of the knee shows a linear radiodensity in the joint space consistent with chondrocalcinosis. What is the most likely diagnosis?

A. Calcium pyrophosphate arthritis (pseudogout)
B. Gout
C. Rheumatoid arthritis
D. Septic arthritis

VIII-82. Mr. Hinsley is a 72-year-old man with only a history of hypertension on hydrochlorothiazide. He presents today with acute, excruciating knee pain. On examination, his knee is warm, mildly erythematous, swollen, and tender to the touch or passive movement. Microscopic examination of joint fluid is shown in Figure VIII-82A. Which of the following is Mr. Hinsley's most likely metabolic derangement?

A. Acute bacterial joint infection
B. Antibodies to anti-nuclear antigens
C. Hyaline cartilage degeneration
D. Increased production of inorganic pyrophosphate
E. Uric acid overproduction

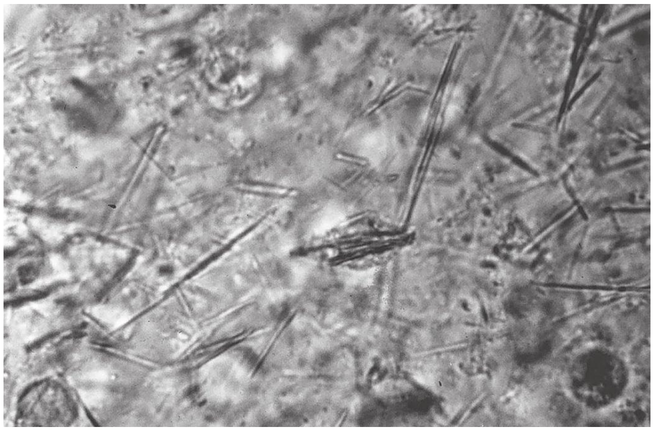


FIGURE VIII-82A

VIII-83. You are planning on starting allopurinol for a 55-year-old woman for a new diagnosis of gouty arthritis. Which of the following statements best describes an appropriate dosing strategy for allopurinol?

A. Allopurinol and azathioprine are commonly used together in the treatment of gout.
B. Allopurinol dosing should be adjusted for liver function.
C. Allopurinol dosing should be titrated to achieve a serum uric acid level <6 mg/dL.
D. Allopurinol should be avoided when patients are taking colchicine.
E. Allopurinol toxicity is more common in patients expressing human leukocyte antigen-B27.

VIII-84. Which of the following findings is typically seen in patients with fibromyalgia?

A. Elevated C-reactive protein
B. Elevated thyroid-stimulating hormone
C. Erosions of the metacarpophalangeal joints on radiographs
D. Positive anti-nuclear antibody
E. Skin roll tenderness on physical examination

VIII-85. A 42-year-old woman is seen in her primary care doctor's office complaining of diffuse pains and fatigue. She has a difficult time localizing the pain to any particular joint or location, but she reports it affects her upper and lower extremities, neck, and hips. It is described as achy and 10 out of 10 in intensity. She feels that her joints are stiff but does not notice that it is worse in the morning. The pain has been present for the last 6 months and is increasing in intensity. She has tried both over-the-counter ibuprofen and acetaminophen without significant relief. The patient feels as if the pain is interfering with her ability to get restful sleep and is making it difficult for her to concentrate. She has missed multiple days of work as a waitress and fears that she will lose her job. There is a medical history of depression and obesity. The patient is currently taking venlafaxine sustained release 150 mg daily. She has a family history of rheumatoid arthritis in her mother. She smokes one pack of cigarettes daily.

On physical examination, vital signs are normal. Body mass index is 36 kg/m^2. Joint examination demonstrates no erythema, swelling, or effusions. There is diffuse pain with palpation at the insertion points of the suboccipital muscles, at the midpoint of the upper border of the trapezius muscle, along the second costochondral junction, at the lateral epicondyles, and along the medial fat pad of the knees. All of the following statements regarding the cause of this patient's diffuse pain syndrome are true EXCEPT:

A. Cognitive dysfunction, sleep disturbance, anxiety, and depression are common comorbid neuropsychological conditions.
B. Pain in this syndrome is associated with increased evoked pain sensitivity.
C. Pain in this syndrome is often localized to specific joints.
D. This syndrome is present in 2–5% of the general population, but increases in prevalence to 20% or more of patients with degenerative or inflammatory rheumatic disorders.
E. Women are nine times more likely than men to be affected by this syndrome.

VIII-86. A 36-year-old woman presents to your office with diffuse pain throughout her body associated with fatigue, insomnia, and difficulty concentrating. She finds the pain difficult to localize but reports that it is 7–8 out of 10 in intensity and not relieved by nonsteroidal anti-inflammatory medications. She has a long-standing history of generalized anxiety disorder and is treated with sertraline 100 mg daily as well as clonazepam 1 mg twice daily. On examination, she has pain with palpation at several musculoskeletal sites. Her laboratory examination demonstrates a normal complete blood count, basic metabolic panel, erythrocyte sedimentation rate, and rheumatoid factor. You diagnose her with fibromyalgia. All of the following therapies are recommended as part of the treatment plan for fibromyalgia EXCEPT:

A. An exercise program that includes strength training, aerobic exercise, and yoga
B. Cognitive-behavioral therapy for insomnia
C. Milnacipran
D. Oxycodone
E. Pregabalin

VIII-87. Which of the following conditions is the most frequent cause of neuropathic joint disease (Charcot joint)?

A. Amyloidosis
B. Congenital indifference to pain
C. Diabetes mellitus
D. Syringomyelia
E. Tabes dorsalis

VIII-88. A 42-year-old man is found to have the finding seen in Figure VIII-88 on a physical examination. All of the following conditions are associated with this finding EXCEPT:

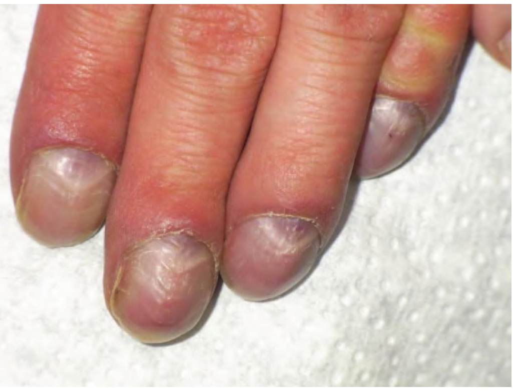


FIGURE VIII-88 Reproduced with permission from Kang S et al: *Fitzpatrick's Dermatology*, 9th ed. New York: McGraw Hill, 2019.

A. Chronic obstructive pulmonary disease
B. Cyanotic congenital heart disease
C. Cystic fibrosis
D. Hepatocellular carcinoma
E. Hyperthyroidism

VIII-89. A 52-year-old man presented to his primary care physician complaining of new-onset pain in the knuckles of his index and middle fingers of both hands. On examination, the second and third metacarpophalangeal (MCP) joints of both hands are swollen and tender. The rest of his physical examination is normal. His past medical history is only notable for hyperlipidemia controlled with atorvastatin. His laboratory studies are notable for an elevated ferritin, and after demonstration of a mutation of the HFE gene, he is diagnosed with hemochromatosis. Which of the following statements regarding his joint abnormalities is true?

A. The second and third finger MCPs are also typically involved in osteoarthritis.
B. Arthropathy is unlikely related to hemochromatosis.
C. Arthropathy may progress with phlebotomy.
D. Arthropathy occurs in less than 20% of patients with hemochromatosis.
E. Radiographs are likely to show erosions in the MCPs.

VIII-90. All of the following can cause bursitis EXCEPT:

A. Bacterial infection
B. Fibromyalgia
C. Gout
D. Rheumatoid arthritis
E. Overuse

VIII-91. A 57-year-old man comes to the clinic with new pain in his right elbow. He works for an international corporation and travels frequently for work. This travel requires him to carry and pull suitcases through the airport on his weekly trips out of town. He notes that the pain is worse when shaking hands at business meetings. On examination, no swelling is noted in the elbow or other joints. The pain is reproducible by palpation of the lateral elbow. Which of the following is an option for treatment of his musculoskeletal condition?

A. Adalimumab
B. Corticosteroid injection at the lateral epicondyle
C. Methotrexate
D. Nonsteroidal anti-inflammatory drugs and rest
E. B and D

VIII-92. A 32-year-old woman is seen in the clinic with a complaint of left knee pain. She enjoys running long distances and is currently training for a marathon. She is running on average 30–40 miles weekly. She currently is experiencing an aching pain on the lateral aspect of her left knee. There is a burning sensation that also continues up the lateral aspect of her thigh. She denies any injury to her knee, and she has not felt that it was hot or swollen. She is otherwise healthy and takes no medications other than herbal supplements. Physical examination of the knee reveals point tenderness over the lateral femoral condyle that is worse with flexing the knee. The patient is asked to lie on her right side with her right knee and hip flexed at 90 degrees. Her left leg is extended at the hip and slowly lowered into adduction behind the bottom leg, reproducing the patient's left knee pain. All of the following treatments can be recommended for this patient EXCEPT:

A. Assessment of the patient's running shoes to ensure a proper fit
B. Glucocorticoid injection so as not to interfere with the patient's continued preparation for the upcoming marathon
C. Ibuprofen 600–800 mg every 6 hours as needed for pain
D. Referral for physical therapy
E. Referral for surgical release if conservative therapy fails

VIII-93. A 58-year-old woman presents complaining of right shoulder pain. She does not recall any prior injury but notes that she feels that the shoulder has been getting progressively stiffer over the last several months. She previously had several episodes of bursitis of the right shoulder that were treated successfully with nonsteroidal anti-inflammatory drugs and corticosteroid injections. The patient's past medical history is also significant for diabetes mellitus, for which she takes metformin and glyburide. On physical examination, the right shoulder is not warm or red but is tender to touch. Passive and active range of motion are limited in flexion, extension, and abduction. A right shoulder radiogram shows osteopenia without evidence of joint erosion or osteophytes. What is the most likely diagnosis?

A. Adhesive capsulitis
B. Avascular necrosis
C. Bicipital tendinitis
D. Osteoarthritis
E. Rotator cuff tear

VIII-94. A 32-year-old woman presents to the clinic with right thumb and wrist pain that has worsened over several weeks. She has pain when she pinches her thumb against her other fingers. Her only other history is that she is a new mother with an 8-week-old infant at home. On physical examination, she has mild swelling and tenderness over the radial styloid process, and pain is elicited when she places her thumb in her palm and grasps it with her fingers. A Phalen maneuver is negative. Which condition is most likely?

A. Carpal tunnel syndrome
B. De Quervain tenosynovitis
C. Gouty arthritis of the first metacarpophalangeal joint
D. Palmar fasciitis
E. Rheumatoid arthritis

VIII-95. You are evaluating a 42-year-old woman who complains of pain on the underside of her right heel that is excruciating in the morning when she first walks from bed to the bathroom. The pain improves somewhat during the morning but again worsens mid-day particularly when climbing stairs. She has a past medical history of hypertension, smokes one pack per day of cigarettes, and works as a waitress at a diner. Medications include hydrochlorothiazide and oral contraceptives. Physical examination is unremarkable except for flat feet and focal tenderness on the bottom of the right heel. There is no tenderness at the ankle or calf, and the diameters of the lower legs are equivalent. A radiograph of the right heel and ankle shows only heel spurs. All of the following statements regarding her condition are true EXCEPT:

A. Heel spurs are not diagnostic.
B. Local glucocorticoid injection incurs a risk of plantar fascia rupture.
C. Oral contraceptives and smoking are risk factors.
D. Orthotic shoe implants may be beneficial.
E. The prognosis for improvement is good.

ANSWERS

VIII-1. **The answer is B.** *(Chap. 342)* Inflammatory reactions initiated by mononuclear leukocytes and not by antibody alone have been termed delayed-type hypersensitivity reactions. The term delayed has been used to contrast a cellular response that appears 48–72 hours after antigen exposure with an immediate hypersensitivity response generally seen within 12 hours of antigen challenge and initiated by basophil mediator release or preformed antibody. In patients previously infected with *Mycobacterium tuberculosis*, intradermal placement of tuberculin purified protein derivative as a skin test challenge results in an indurated area of skin in 48–72 hours, reflecting a delayed type hypersensitivity reaction by leukocytes. Immune complex formation refers to antigen, complement and antibody coming together to clear antigen, but can also lead to tissue damage when not cleared by the reticuloendothelial system and deposited in tissues like the blood vessels or glomeruli as can occur in some vasculitis syndromes. Cytotoxic reactions to antibody occur when antibodies against cells or tissues bind complement and lead to cell lysis or tissue injury, as occurs in transfusion reactions.

VIII-2. **The answer is A.** *(Chap. 342)* The innate immune system is phylogenetically the oldest form of immunologic defense system, inherited from invertebrates. This defense system uses germline-encoded proteins to recognize pathogen-associated molecular patterns. Cells of the innate immune system include macrophages, dendritic cells, and natural killer lymphocytes. The critical components of the innate immune system include recognition by germline-encoded host molecules and recognition of key microbe virulence factors, but there is no recognition of self-molecules and of benign foreign molecules or microbes. Adaptive immunity is found only in vertebrate animals and is based on the generation of antigen receptors on T and B lymphocytes by gene rearrangements, such that individual T or B cells express unique antigen receptors on their surface capable of recognizing diverse environmental antigens.

VIII-3. **The answer is A.** *(Chap. 342)* Complement activity, which results from the sequential interaction of a large number of plasma and cell membrane proteins, plays an important role in the inflammatory response. The classic pathway of complement activation is initiated by an antibody antigen interaction. The first complement component (C1, a complex composed of three proteins) binds to immune complexes with activation mediated by C1q. Active C1 then initiates the cleavage and concomitant activation of components C4 and C2. The activated C1 is destroyed by a plasma protease inhibitor termed C1 esterase inhibitor. This molecule also regulates clotting factor XI and kallikrein. Patients with a deficiency of C1 esterase inhibitor may develop angioedema, sometimes leading to death by asphyxia. Attacks may be precipitated by stress or trauma. In addition to low antigenic or functional levels of C1 esterase inhibitor, patients with this autosomal dominant condition may have normal levels of C1 and C3 but low levels of C4 and C2. Danazol therapy produces a striking increase in the level of this important inhibitor and alleviates the symptoms in many patients. An acquired form of angioedema caused by a deficiency of C1 esterase inhibitor has been described in patients with autoimmune or malignant disease.

VIII-4. **The answer is A.** *(Chaps. 343 and 355)* Although the associations of human disease with particular human leukocyte antigen (HLA) alleles or haplotypes primarily involve the class II region, there are also several prominent disease associations with class I alleles. Ankylosing spondylitis has a strong association with HLA-B27, a class I major histocompatibility complex (MHC) molecule. Celiac disease, rheumatoid arthritis, and type 1 diabetes are associated with particular HLA-DQ and/or HLA-DR alleles, which are class II MHC alleles. Huntington disease has autosomal dominant Mendelian inheritance.

VIII-5. **The answer is C.** *(Chap. 343)* The human major histocompatibility complex (MHC) genes are located on a 4-megabase region on chromosome 6. The major function of the MHC complex genes is to produce proteins that are important in developing immunologic specificity through their role in binding antigen for presentation to T cells. This process is nonspecific, and the ability of a human leukocyte antigen molecule to bind to a particular protein depends on the molecular fit between the amino acid sequence of a particular protein and the corresponding domain on the MHC molecule. Once a peptide has bound, the MHC-peptide complex binds to the T-cell receptor, after which the T cell must determine whether an immune response should be generated. If an antigen is similar to an endogenous protein, the potential antigen will be recognized as a self-peptide, and tolerance to the antigen will be continued. The MHC I and II complexes have been implicated in the development of many autoimmune diseases, which occur when T cells fail to recognize a peptide as a self-peptide and an immune response is allowed to develop. MHC I and II genes also play a major role in tissue compatibility for transplantation and are important in generating immune-mediated rejection. The other options listed as answers refer to functions of immunoglobulins. The variable region of the immunoglobulin is a B-cell–specific response to an antigen to promote neutralization of the antigen through agglutination and precipitation. The constant region of the immunoglobulin is able to nonspecifically activate the immune system through complement activation and promotion of phagocytosis by neutrophils and macrophages.

VIII-6. **The answer is E.** *(Chaps. 344 and 342)* Hundreds of gene products have been characterized as effectors or mediators of the immune system. Whenever the expression or function of one of these products is genetically impaired (provided the function is nonredundant), a primary immunodeficiency (PID) occurs. PIDs are genetic diseases with primarily Mendelian inheritance. More than 250 conditions have now been described, and deleterious mutations in approximately 210 genes have been identified (Table VIII-6). The overall prevalence of PIDs has been estimated in various countries at 5 per 100,000 individuals; however, given the difficulty in diagnosing these rare and complex diseases, this figure is probably an underestimate. PIDs can involve all possible aspects of immune responses, from innate through adaptive, cell differentiation, and effector function and regulation. For the sake of clarity, PIDs should be classified according to (1) the arm of the immune system that is defective and (2) the mechanism of the defect (when known). The consequences of PIDs vary widely as a function of the molecules that are defective. This concept translates into multiple levels of vulnerability to infection by pathogenic and opportunistic micro-organisms, ranging from extremely broad (as in severe combined immunodeficiency) to narrowly restricted to a single micro-organism (as in Mendelian susceptibility to mycobacterial disease). The locations of the sites of infection and the causal micro-organisms involved will thus help physicians arrive at proper diagnoses. PIDs can also lead to immunopathologic responses such as allergy (as in Wiskott-Aldrich syndrome), lymphoproliferation, and autoimmunity. A combination of recurrent infections, inflammation, and autoimmunity can be observed in a number of PIDs, thus creating obvious therapeutic challenges. The most frequent symptom prompting the diagnosis of a PID is the presence of recurrent or unusually severe infections. Infections of the respiratory tract (bronchi, sinuses) mostly suggest a defective antibody response. In general, invasive bacterial infections can result from complement deficiencies, signaling defects of innate immune responses, asplenia, or defective antibody responses. Viral infections, recurrent *Candida* infections, and opportunistic infections are generally suggestive of impaired T-cell immunity. Skin infections and deep-seated abscesses primarily reflect innate immune defects (such as chronic granulomatous disease); however, they may also appear in the autosomal dominant hyper-IgE syndrome. Finally, some PIDs increase the risk of cancer, notably but not exclusively lymphocytic cancers (e.g., lymphoma).

VIII-7. **The answer is B.** *(Chap. 374)* This patient has axillary folliculitis, an infection of the hair follicles. Based on his history, including recurrent infections with the catalase-positive organism, *Serratia marcescens*, he most likely has chronic granulomatous disease (CGD). CGDs are characterized by impaired phagocytic killing of micro-organisms by neutrophils and macrophages. About 70% of cases are associated with X-linked recessive

TABLE VIII-6 **Classification of Primary Immune Deficiency Diseases**

Deficiencies of the Innate Immune System	
• Phagocytic cells: - Impaired production: severe congenital neutropenia - Asplenia - Impaired adhesion: leukocyte adhesion deficiency - Impaired killing: chronic granulomatous disease • Innate immunity receptors and signal transduction: - Defects in Toll-like receptor signaling - Mendelian susceptibility to mycobacterial disease • Complement deficiencies: - Classical, alternative, and lectin pathways - Lytic phase	
Deficiencies of the Adaptive Immune System	
• T lymphocytes: - Impaired development - Impaired survival, migration, function	Severe combined immune deficiencies DiGeorge syndrome Combined immunodeficiencies Hyper-IgE syndrome (autosomal dominant) DOCK8 deficiency CD40 ligand deficiency Wiskott-Aldrich syndrome Ataxia-telangiectasia and other DNA repair deficiencies
• B lymphocytes: - Impaired development - Impaired function	XL and AR agammaglobulinemia Hyper-IgM syndrome Common variable immunodeficiency IgA deficiency
Regulatory Defects	
• Innate immunity	Autoinflammatory syndromes (outside the scope of this chapter)
• Adaptive immunity	Severe colitis Hemophagocytic lymphohistiocytosis Autoimmune lymphoproliferation syndrome Autoimmunity and inflammatory diseases (IPEX, APECED)

Abbreviations: APECED, autoimmune polyendocrinopathy candidiasis ectodermal dysplasia; AR, autosomal recessive; IPEX, immunodysregulation polyendocrinopathy enteropathy X-linked syndrome; XL, X-linked.

inheritance versus autosomal inheritance in the remaining 30%. CGD causes deep tissue bacterial and fungal abscesses in macrophage-rich organs such as the skin, lymph nodes, liver, and lungs. Recurrent skin infections, such as folliculitis, are common and can prompt an early diagnosis of CGD. The infectious agents are typically catalase-positive bacteria (such as *Staphylococcus aureus* and *Staphylococcus marcescens*) but also include *Burkholderia cepacia*, pathogenic mycobacteria (in certain regions of the world), and fungi (mainly filamentous molds, such as *Aspergillus*). CGD is caused by defective production of reactive oxygen species (ROS) in the phagolysosome membrane following phagocytosis of micro-organisms. Diagnosis of CGD is based on assays of ROS production in neutrophils and monocytes such as the dihydrorhodamine fluorescence or nitroblue tetrazolium assays. CGD is a granulomatous disease with macrophage-rich granulomas in the liver, spleen, and other organs. These are sterile granulomas that cause disease by obstruction (bladder, pylorus, etc.) or inflammation (colitis, restrictive lung disease). The treatment of bacterial infections is generally based on combination therapy with antibiotics that are able to penetrate into cells. The treatment of fungal infections requires aggressive, long-term use of antifungals. Inflammatory/granulomatous lesions are usually steroid sensitive; however, glucocorticoids often contribute to the spread of infections. The treatment of CGD mostly relies on preventing infections. It has been unambiguously demonstrated that prophylactic use of trimethoprim/sulfamethoxazole is both well tolerated and highly effective in reducing the risk of bacterial infection. Daily administration of azole derivatives (notably itraconazole) also reduces the frequency of fungal complications. Human stem cell transplantation is an established curative approach for CGD; however, the risk-benefit ratio must be carefully assessed on a case-by-case basis. Gene therapy approaches are also being evaluated.

VIII-8. **The answer is D.** *(Chap. 345)* The patient has a history consistent with allergic rhinitis. Episodic rhinorrhea; sneezing; obstruction of the nasal passages with lacrimation; and pruritus of the conjunctiva, nasal mucosa, and oropharynx are the hallmarks of allergic rhinitis. Allergic rhinitis generally occurs in atopic individuals, often in association with atopic dermatitis, food allergy, urticaria, and/or asthma. Up to 50% of patients with allergic rhinitis manifest asthma, whereas 70–80% of individuals with asthma and 80% of individuals with chronic bilateral sinusitis experience allergic rhinitis. Female sex, particulate air pollution exposure, and maternal tobacco smoking increase the risk of developing allergic rhinitis over the life span. Psoriasis is an autoimmune skin disease that is not associated with a history of atopy or allergic rhinitis.

VIII-9. **The answer is D.** *(Chap. 345)* This patient presents with symptoms of cold urticaria, an IgE-dependent urticarial reaction to cold exposure. After exposure to cold, urticarial lesions appear in exposed areas and usually last for <2 hours. Histologic examination of the urticarial lesion would demonstrate mast cell degranulation with edema of the dermis and subcutaneous tissues. In experimental exposure to a cold challenge such as an ice water bath, elevated levels of histamine in venous blood may be demonstrated if assessed in the extremity exposed to a cold environment, whereas the histamine levels would be normal in a nonexposed extremity. The appearance of a linear wheal after a firm stroke is indicative of dermatographism. This condition can be seen in 1–4% of the population and is often found in individuals with cold urticaria. In general, cold urticaria is a localized process without adverse consequences. However, vascular collapse may occur if an individual is submerged in cold water. Many individuals request treatment because they are embarrassed by their condition or are symptomatic from recurrent urticaria and pruritus. Treatment with H_1 histamine receptor blockers is usually adequate for symptom control. Cyproheptadine or hydroxyzine can be added to therapy if H_1 antihistamines are inadequate. In this patient, there is a clear precipitant for developing urticaria—cold exposure. Thus, no other evaluation is necessary. In the evaluation and management of chronic urticaria, identification and elimination of precipitating factors are important. Possible etiologic factors include foods, pollens, molds, and medications. In this case, the urticaria predates the use of oral contraceptive medications; thus, stopping oral contraceptives would be unlikely to be helpful. Assessment of antithyroglobulin and antimicrosomal antibodies can be helpful in individuals with chronic urticaria in whom a cause is not otherwise identified. Deficiency of C1 or the presence of a C1 inhibitor presents as recurrent angioedema rather than urticaria.

VIII-10. **The answer is A.** *(Chap. 346)* Anaphylaxis is a potentially life-threatening systemic allergic reaction involving one or more organ systems that typically occurs within seconds to minutes of exposure to the anaphylactic trigger, most often a drug, food, or Hymenoptera sting. The patient was exposed to iodinated contrast and ceftriaxone 2 weeks before the incident with no repeat exposure indicating that these agents were not the cause of anaphylaxis. Recombinant biologics can induce the formation of IgE against the proteins or against glycosylated structures that serve as immunogens. More recently, outbreaks of anaphylaxis to the EGFR antibody, cetuximab, were reported in association with elevated titers of serum IgE to alpha-1,3-galactose (alpha-gal), an oligosaccharide found in nonprimate mammals. Cetuximab is derived from a mouse cell line expressing a transferase that tags the Fab′ portion of the cetuximab heavy chain with alpha-gal. Interestingly, patients with a history of multiple bites from *Amblyomma americanum* ticks commonly found in the Carolinas, Arkansas, and Tennessee are more likely to have anti–alpha-gal IgE compared with control patients living outside those states. Such individuals who become sensitized to alpha-gal can develop episodes of delayed anaphylaxis to beef, lamb, and pork. Antibiotics and iodinated contrast are other potential causes of anaphylaxis, but given the patient’s treatment with cetuximab, geographic region, and triggering event of consuming beef, alpha-gal-induced anaphylaxis is most likely. Lisinopril can cause angioedema through reduced catabolism of bradykinin, a different pathogenesis than anaphylaxis.

VIII-11. The answer is E. *(Chap. 346)* There is no convincing evidence that age, sex, race, or geographic location predisposes a human to anaphylaxis except through exposure to specific immunogens. According to most studies, atopy does not predispose individuals to anaphylaxis from penicillin therapy or venom of a stinging insect but is a risk factor for allergens in food or latex. Risk factors for a poor outcome, however, include older age, use of beta blockers, and the presence of pre-existing asthma. Individuals differ in the time of appearance of symptoms and signs, but the hallmark of the anaphylactic reaction is the onset of some manifestation within seconds to minutes after introduction of the antigen. Early recognition of an anaphylactic reaction is mandatory, because death can occur within minutes to hours after the first symptoms due to shock. Mild symptoms such as pruritus and urticaria can be controlled by administration of 0.3–0.5 mL of 1:1000 (1 mg/mL) epinephrine subcutaneously or IM, with repeated doses as required at 5- to 20-minute intervals for a severe reaction. The failure to use epinephrine within the first 20 minutes of symptoms is a risk factor for poor outcome in studies of anaphylaxis to food. An IV infusion should be initiated to provide a route for administration of 2.5 mL epinephrine, diluted 1:10,000, at 5- to 10-minute intervals, volume expanders such as normal saline, and vasopressor agents such as dopamine if intractable hypotension occurs. Replacement of intravascular volume due to postcapillary venular leakage may require several liters of saline. Epinephrine provides both α- and β-adrenergic effects, resulting in vasoconstriction, bronchial smooth muscle relaxation, and attenuation of enhanced venular permeability. Ancillary agents such as the antihistamine diphenhydramine 50–100 mg IM or IV, and aminophylline 0.25–0.5 g IV, are appropriate for urticaria-angioedema and bronchospasm, respectively. IV glucocorticoids (0.5–1 mg/kg of methylprednisolone) are not effective for the acute event but may alleviate later recurrence of bronchospasm, hypotension, or urticaria.

VIII-12. The answer is B. *(Chap. 347)* This patient has mastocytosis, which is defined by accumulation of clonally expanded mast cells in tissues such as skin, bone marrow, liver, spleen, and gut. The mast cell expansion is generally recognized in skin and/or bone marrow. Mastocytosis can be limited to the skin (cutaneous mastocytosis) or can be systemic. Systemic mastocytosis (SM) refers to involvement of a noncutaneous site(s). The clinical manifestations of SM are due to the release of bioactive substances acting at both local and distal sites, tissue occupancy by the mast cell mass, and the tissue response to that mass. The pharmacologically induced manifestations are intermittent flushing, tachycardia and vascular collapse, gastric distress, lower abdominal crampy pain, and diarrhea. The periportal fibrosis associated with mast cell infiltration and a prominence of eosinophils may lead to portal hypertension and ascites. In some patients, anaphylaxis with rapid and life-threatening vascular collapse can be induced by Hymenoptera stings. These patients often have evidence of venom-specific IgE. The neuropsychiatric disturbances are clinically most evident as impaired recent memory, decreased attention span, and "migraine-like" headaches. Patients may experience exacerbation of a specific clinical sign or symptom variably with alcohol ingestion, temperature changes, stress, use of mast cell–interactive opioids, or ingestion of nonsteroidal anti-inflammatory drugs. Mastocytosis occurs at any age and has a slight preponderance in males. Cutaneous mastocytosis is diagnosed by observing the characteristic lesions of maculopapular cutaneous mastocytosis or mastocytoma(s). A skin biopsy can be obtained to confirm the diagnosis. Although the diagnosis of SM is generally suspected on the basis of the clinical history and physical findings, and can be supported by laboratory procedures (such as the elevated serum tryptase in this case), it can be established only by a tissue diagnosis. A neutrophilic dermal infiltrate is seen in Sweet syndrome and other neutrophilic dermatoses. Non-caseating granulomas can be seen in cutaneous sarcoid. An interface dermatitis is noted in a variety of conditions including cutaneous lupus, dermatomyositis, and some infections. Spongiotic changes in the epidermis are characteristic of eczematous dermatitis.

VIII-13. The answer is B. *(Chap. 348)* The mechanisms of tissue injury in autoimmune diseases can be divided into antibody-mediated and cell-mediated processes (Table VIII-13).

TABLE VIII-13 Mechanisms of Tissue Damage in Autoimmune Disease

Effector	Mechanism	Target	Disease
Autoantibody	Blocking or inactivation	α Chain of the nicotinic acetylcholine receptor	Myasthenia gravis
		Phospholipid–β_2-glycoprotein I complex	Antiphospholipid syndrome
		Insulin receptor	Insulin-resistant diabetes mellitus
		Intrinsic factor	Pernicious anemia
	Stimulation	TSH receptor (LATS)	Graves disease
		Proteinase-3 (ANCA)	Granulomatosis with polyangiitis
		Epidermal cadherin	Pemphigus vulgaris
		Desmoglein 3	
	Complement activation	α_3 Chain of collagen IV	Goodpasture syndrome
	Immune complex formation	Double-stranded DNA	Systemic lupus erythematosus
		Immunoglobulin	Rheumatoid arthritis
	Opsonization	Platelet GpIIb:IIIa	Autoimmune thrombocytopenic purpura
		Rh antigens, I antigen	Autoimmune hemolytic anemia
	Antibody-dependent cellular cytotoxicity	Thyroid peroxidase, thyroglobulin	Hashimoto thyroiditis
T cells	Cytokine production		Rheumatoid arthritis, multiple sclerosis, type 1 diabetes mellitus
	Cellular cytotoxicity		Type 1 diabetes mellitus

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; LATS, long-acting thyroid stimulator; TSH, thyroid-stimulating hormone.

The pathogenicity of autoantibodies can be mediated through several mechanisms, including opsonization of soluble factors or cells, activation of an inflammatory cascade via the complement system, and interference with the physiologic function of soluble molecules or cells. Goodpasture syndrome, a disease characterized by lung hemorrhage and severe glomerulonephritis, represents an example of antibody binding leading to local activation of complement and neutrophil accumulation and activation. The autoantibody in this disease binds to the α_3 chain of type IV collagen in the basement membrane.

VIII-14. **The answer is E.** *(Chap. 348)* Derangements of normal processes may predispose to the development of autoimmunity (Table VIII-14). In general, these abnormal responses require both an exogenous trigger, such as infection (bacterial or viral) or cigarette smoking, and the presence of endogenous abnormalities in the cells of the immune system. One of the best examples of autoreactivity and autoimmune disease resulting from molecular mimicry is rheumatic fever, in which antibodies to the M protein of streptococci cross-react with myosin, laminin, and other matrix proteins as well as with neuronal antigens. Deposition of these autoantibodies in the heart initiates an inflammatory response, whereas their penetration into the brain can result in Sydenham chorea. Molecular mimicry between microbial proteins and host tissues has been reported in type 1 diabetes mellitus, rheumatoid arthritis, celiac disease, and multiple sclerosis.

VIII-15. **The answer is D.** *(Chap. 349)* Drug-induced lupus (DIL) is a syndrome of positive antinuclear antibody (ANA) associated with symptoms such as fever, malaise, arthritis or intense arthralgias/myalgias, serositis, and/or rash. The syndrome appears during therapy with certain medications and biologic agents, is predominant in whites, has less female predilection than systemic lupus erythematosus, rarely involves kidneys or brain, is rarely associated with anti-dsDNA, is commonly associated with antibodies to histones, and usually resolves over several weeks after discontinuation of the offending

TABLE VIII-14 Mechanisms of Autoimmunity

I. Exogenous
  A. Molecular mimicry
  B. Superantigenic stimulation
  C. Microbial and tissue damage–associated adjuvanticity
II. Endogenous
  A. Altered antigen presentation
    1. Loss of immunologic privilege
    2. Presentation of novel or cryptic epitopes (epitope spreading)
    3. Alteration of self-antigen
    4. Enhanced function of antigen-presenting cells
      a. Costimulatory molecule expression
      b. Cytokine production
  B. Increased T-cell help
    1. Cytokine production
    2. Costimulatory molecules
  C. Increased B-cell function
    1. B-cell activating factor
    2. Costimulatory molecules
  D. Apoptotic defects or defects in clearance of apoptotic material
  E. Cytokine imbalance
  F. Altered immunoregulation

medication. The list of substances that can induce lupus-like disease is long. Among the most frequent are the antiarrhythmics procainamide, disopyramide, and propafenone; the anti-hypertensive hydralazine; several angiotensin-converting enzyme inhibitors and beta blockers; the antithyroid propylthiouracil; the antipsychotics chlorpromazine and lithium; the anticonvulsants carbamazepine and phenytoin; the antibiotics isoniazid, minocycline, and nitrofurantoin (Macrodantin); the antirheumatic sulfasalazine; the diuretic hydrochlorothiazide; and the antihyperlipidemics lovastatin and simvastatin. Biologics that can cause DIL include inhibitors of interferons and tumor necrosis factor. In DIL, ANA usually appears before symptoms; however, many of the medications mentioned above induce ANA in patients who never develop symptoms of DIL. It is appropriate to test for ANA at the first hint of relevant symptoms and to use test results to help decide whether to withdraw the suspect agent. Anti-β-2-glycoprotein antibodies are noted in antiphospholipid antibody syndrome. Anti–cyclic citrullinated protein antibodies are characteristic of rheumatoid arthritis and are not commonly present in patients with psoriasis or psoriatic arthritis. Anti-thyroid peroxidase antibodies are seen in Hashimoto thyroiditis.

VIII-16. The answer is A. *(Chap. 349)* Systemic lupus erythematosus (SLE) is a multigenic disease characterized by an abnormal immune response (Figure VIII-16). Rare single-gene defects confer high hazard ratios (HRs) for SLE (5–25), including homozygous deficiencies of early components of complement (C1q,r,s; C2; C4) and a mutation in *TREX1* (encoding a DNase) on the X chromosome. C1-esterase inhibitor deficiency is associated with hereditary angioedema rather than SLE. Predisposing, antigen-presenting human leukocyte antigen (HLA) molecules are most commonly found in multiple ethnic groups (HLA-DRB1 *0301 and *1501 and DR3), as well as multiple genes across the major histocompatibility complex 120-gene region. Female sex is permissive for SLE with evidence for hormone effects, genes on the X chromosome, and epigenetic differences between genders playing a role. Females of many mammalian species make higher antibody responses than males. Women exposed to estrogen-containing oral contraceptives or hormone replacement have an increased risk of developing SLE (HR 1.2–2). Several environmental stimuli may influence SLE. Exposure to ultraviolet light causes flares of SLE in ~70% of patients, possibly by increasing apoptosis in skin cells or by altering DNA and intracellular proteins to make them antigenic.

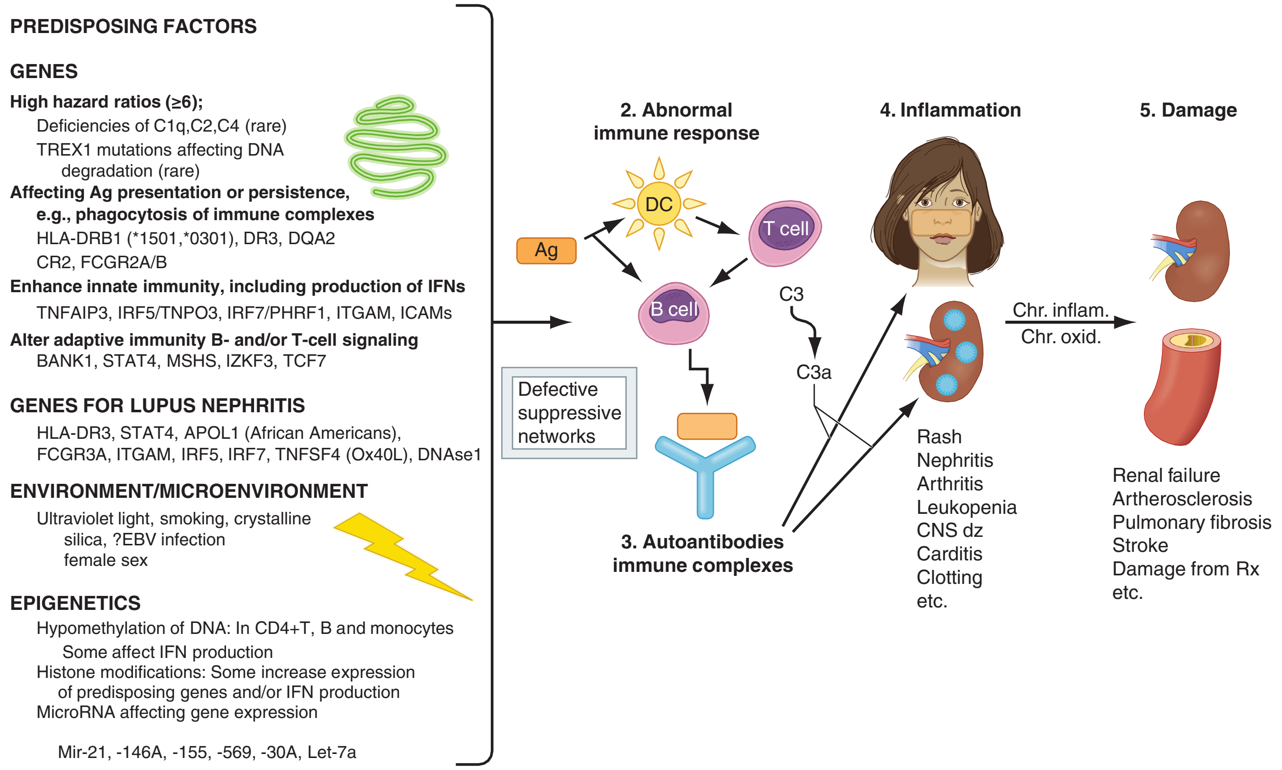

PREDISPOSING FACTORS
GENES
High hazard ratios (≥6);
Deficiencies of C1q,C2,C4 (rare)
TREX1 mutations affecting DNA degradation (rare)
Affecting Ag presentation or persistence, e.g., phagocytosis of immune complexes
HLA-DRB1 (*1501,*0301), DR3, DQA2
CR2, FCGR2A/B
Enhance innate immunity, including production of IFNs
TNFAIP3, IRF5/TNPO3, IRF7/PHRF1, ITGAM, ICAMs
Alter adaptive immunity B- and/or T-cell signaling
BANK1, STAT4, MSHS, IZKF3, TCF7
GENES FOR LUPUS NEPHRITIS
HLA-DR3, STAT4, APOL1 (African Americans), FCGR3A, ITGAM, IRF5, IRF7, TNFSF4 (Ox40L), DNAse1
ENVIRONMENT/MICROENVIRONMENT
Ultraviolet light, smoking, crystalline silica, ?EBV infection
female sex
EPIGENETICS
Hypomethylation of DNA: In CD4+T, B and monocytes
Some affect IFN production
Histone modifications: Some increase expression of predisposing genes and/or IFN production
MicroRNA affecting gene expression
Mir-21, -146A, -155, -569, -30A, Let-7a
2. Abnormal immune response
Ag
DC
T cell
B cell
Defective suppressive networks
C3
C3a
3. Autoantibodies immune complexes
4. Inflammation
Rash
Nephritis
Arthritis
Leukopenia
CNS dz
Carditis
Clotting
etc.
Chr. inflam.
Chr. oxid.
5. Damage
Renal failure
Atherosclerosis
Pulmonary fibrosis
Stroke
Damage from Rx
etc.

FIGURE VIII-16. *Abbreviations:* Ag, antigen; C1q, complement system; C3, complement component; CNS, central nervous system; chr, chronic; DC, dendritic cell; dz, disease; EBV, Epstein-Barr virus; HLA, human leukocyte antigen; IFN, interferon; inflam., inflammation; oxid., oxidation; Rx, prescription.

VIII-17. **The answer is A.** *(Chap. 349)* The patient has Libman-Sacks endocarditis associated with her systemic lupus erythematosus (SLE). This results in fibrinous endocarditis and can lead to valvular insufficiencies, most often mitral or aortic, or embolism. It is not generally found with concomitant pericarditis, although this is another common cardiac manifestation of SLE. Although glucocorticoids and anti-inflammatory therapies have no proven benefit in this condition, they are often used in conjunction with supportive care. Because Libman-Sacks endocarditis is a culture-negative endocarditis and is not thought to be due to microbial infection, blood cultures will not be positive.

VIII-18. **The answer is C.** *(Chap. 349)* This patient is presenting with acute lupus nephritis with evidence of hematuria, proteinuria, and an acute rise in creatinine. Together with infection, nephritis is the most common cause of mortality in the first decade after diagnosis of systemic lupus erythematosus (SLE) and warrants prompt immunosuppressive therapy. It is important to assess for other potentially reversible causes of acute renal insufficiency, but this patient is not otherwise acutely ill and is taking no medications that would cause renal failure. The urinalysis shows evidence of active nephritis with hematuria and proteinuria. Even in the absence of red blood cell casts, therapy should not be withheld to await biopsy results in someone with a known diagnosis of SLE with consistent clinical presentation and urinary findings. This patient also has other risk factors known to predict the development of lupus nephritis, including high titers of anti-dsDNA and African American race. The mainstay of treatment for any life-threatening or organ-threatening manifestation of SLE is high-dose systemic glucocorticoids. Addition of cytotoxic or other immunosuppressive agents (cyclophosphamide, azathioprine, mycophenolate mofetil) is recommended to treat serious complications of SLE, but their effects are delayed for 3–6 weeks after initiation of therapy, whereas the effects of glucocorticoids begin within 24 hours. Thus, these agents alone should not be used to treat acute serious manifestations of SLE. The choice of cytotoxic agent is at the discretion of the treating physician. Cyclophosphamide in combination with steroid therapy has been demonstrated to prevent development of end-stage renal disease better than steroids alone. Likewise, mycophenolate also prevents development of end-stage renal disease in combination with glucocorticoids, and some studies suggest that African Americans have a greater response to mycophenolate than to cyclophosphamide. Plasmapheresis is not indicated in the treatment of lupus nephritis but is useful in cases of severe hemolytic anemia or thrombotic thrombocytopenic purpura associated with SLE. Finally, this patient has no acute indication for hemodialysis and, with treatment, may recover renal function.

VIII-19. **The answer is D.** *(Chap. 350)* Antiphospholipid syndrome (APS) is an autoantibody-mediated acquired thrombophilia characterized by recurrent arterial or venous thrombosis and/or pregnancy morbidity (Table VIII-19). The major antiphospholipid autoantibodies detected in patients' sera are directed against phospholipids and/or phospholipid (PL)-binding plasma proteins such as prothrombin and β2 glycoprotein I (β2GPI). PLs are components of the cytoplasmic membrane of all living cells. The antibodies are typically directed against negatively charged PLs including among others cardiolipin, phosphocholine, and phosphatidylserine. The plasma protein β2GPI is a 43-kDa plasma apolipoprotein, which consists of 326 amino acids arranged in five domains (I through V). Domain V forms a positively charged patch, suitable to interact with negatively charged PLs. In plasma, β2GPI has a circular conformation with domain V binding to and concealing the B-cell epitopes lying on domain I. Another group of antibodies termed *lupus anticoagulant* prolongs clotting times, including activated partial thromboplastin time in vitro, which are not corrected by adding normal plasma. Patients with APS often possess antibodies recognizing *Treponema pallidum* PL/cholesterol complexes, detected by VDRL tests and characterized as biologic false-positive serologic tests for syphilis. The incidence of APS is estimated to be around 5 cases per 100,000 persons per year. Anti-PL antibodies occur in 1–5% of the general population. Their prevalence increases with age; however, it is questionable whether they are able to induce thrombotic events in elderly individuals. Moreover, one-third of patients with systemic lupus erythematosus and other autoimmune diseases possess these antibodies, with only 5–10% of them developing APS.

TABLE VIII-19 **Classification and Nomenclature of Antiphospholipid Antibodies**

Name	Assay for Their Detection	Comments
aCL	ELISA using as antigen CL, a negatively charged phospholipid	aCL from patients with APS recognize β2GPI existing in the human serum as well as in bovine serum, which is used to block the nonspecific binding sites on the ELISA plate. CL simply stabilizes β2GPI at high concentrations on the polystyrene surface.
Antibodies against β2GPI (anti-β2GPI)	ELISA using as antigen affinity purified or recombinant β2GPI in the absence of PL	Antibodies recognize β2GPI bound in the absence of CL to an oxidized polystyrene surface, where oxygen atoms in the moieties C–O or C=O were introduced by γ-irradiation.
LA	aPTT Kaolin clotting time Dilute Russel viper venom test	Antibodies recognize β2GPI or prothrombin and elongate aPTT, implying that they interfere with the generation of thrombin by prothrombin. Prolongation of the clotting times is an in vitro phenomenon, and LA induces thromboses in vivo.

Abbreviations: β2GPI, β2 glycoprotein I; aCL, antibodies against cardiolipin; APL, antiphospholipid syndrome; aPTT, activated partial thromboplastin time; APS, antiphospholipid syndrome; CL, cardiolipin; ELISA, enzyme-linked immunosorbent assay; LA, lupus anticoagulant; PL, phospholipid.

VIII-20. **The answer is A.** *(Chap. 350)* The patient has multiple clinical manifestations of arterial thrombosis in her hand and brain and likely had placental insufficiency in the three prior pregnancies, which makes the diagnosis of antiphospholipid antibody syndrome likely. In addition, she has evidence of acute kidney injury, suggesting multisystem disease. Thrombocytopenia may be due to hemolytic anemia, but the absence of schistocytes makes it less likely that she has thrombotic thrombocytopenic purpura. Although MRI of her brain and extremity duplex may confirm the presence of thrombosis, these will not diagnose antiphospholipid antibody syndrome. An anticardiolipin antibody screening panel will look for evidence of antibodies directed against cardiolipin and β-2 glycoprotein I. Additional testing for lupus anticoagulant determined by clotting assays such as the Russel viper venom time, false-positive rapid plasma reagin, and the activated partial thromboplastin time may also be useful. Antinuclear antibody test is likely to be positive given the common overlap with systemic lupus erythematosus, but it is nonspecific.

VIII-21. The answer is D. *(Chap. 350)* This patient has a typical presentation of antiphospholipid syndrome (APS) with a deep venous thrombosis, history of spontaneous abortion, and isolated elevated activated partial thromboplastin time (aPTT) due to a lupus anticoagulant. Additional clinical features of APS involving the arterial or venous circulation include livedo reticularis (24%), pulmonary embolism (14%), stroke (20%), transient ischemic attack (10%), myocardial infarction (10%), migraine (20%), preeclampsia (10%), thrombocytopenia (30%), and autoimmune hemolytic anemia (10%). Laboratory criteria include demonstration of lupus anticoagulant (elevated aPTT that does not correct on mixing), in conjunction with the presence of anticardiolipin and/or anti-β-2 glycoprotein I on two occasions 3 months apart. After diagnosis of a thrombotic event due to APS, patients should receive warfarin for life with a goal international normalized ratio (INR) of 2.5–3.5 alone or in combination with daily aspirin. During pregnancy, patients should receive heparin plus aspirin. Patients who develop recurrent thrombosis while on effective anticoagulation may benefit from a 5-day infusion of IV gammaglobulin or 4 weeks of rituximab therapy. The optimal therapy for patients with APS without a thrombotic event is not known; however, daily aspirin (80 mg) protects patients with systemic lupus erythematosus and antiphospholipid antibodies from thrombotic events. Warfarin for 3 months with an INR goal of 2.0–3.0 is recommended therapy for deep vein thrombosis (DVT) with a known reversible precipitating event. Warfarin for 6–12 months with an INR goal of 2.0–3.0 is recommended therapy for the first episode of idiopathic DVT.

VIII-22. The answer is D. *(Chap. 351)* Serum antibodies to cyclic citrullinated peptides (anti-CCPs) are routinely included with rheumatoid factor in the diagnostic evaluation of patients with suspected rheumatoid arthritis (RA), and serve as biomarkers of prognostic significance. Anti-CCP antibodies are associated with a higher likelihood of severe disease, including bone erosions and physical disability. Extra-articular manifestations may develop during the clinical course of RA in up to 40% of patients, even prior to the onset of arthritis. Patients most likely to develop extra-articular disease have a history of cigarette smoking, have early-onset significant physical disability, and test positive for serum rheumatoid factor (RF) or anti-CCP antibodies. Rheumatoid vasculitis typically occurs in patients with long-standing disease, a positive test for serum RF or anti-CCP antibodies, and hypocomplementemia. The alleles known to confer the greatest risk of RA are located within the major histocompatibility complex (MHC). It has been estimated that about 13% of the genetic risk for RA resides within this locus. Most, but probably not all, of this risk is associated with allelic variation in the *HLA-DRB1* gene, which encodes the MHC II β-chain molecule. The disease-associated HLA-DRB1 alleles share an amino acid sequence at positions 70–74 in the third hypervariable regions of the HLA-DR β-chain, termed the *shared epitope*. Carriership of the shared epitope alleles is associated with production of anti-CCP antibodies and worse disease outcomes. Some of these HLA-DRB1 alleles bestow a high risk of disease (*0401), whereas others confer a more moderate risk (*0101, *0404, *1001, and *0901). In addition to genetic predisposition, a host of environmental factors have been implicated in the pathogenesis of RA. The most reproducible of these environmental links is cigarette smoking. Numerous cohort and case control studies have demonstrated that smoking confers a relative risk for developing RA of 1.5–3.5. Interestingly, the risk from smoking is almost exclusively related to RF and anti-CCP antibody-positive disease.

VIII-23. The answer is E. *(Chap. 351)* Felty syndrome is defined by the clinical triad of neutropenia, splenomegaly, and nodular rheumatoid arthritis (RA) and is seen in <1% of patients, although its incidence appears to be declining in the face of more aggressive treatment of the joint disease. It typically occurs in the late stages of severe RA and is more common in whites than other racial groups. T-cell large granular lymphocyte leukemia (T-LGL) may have a similar clinical presentation and often occurs in association with RA. T-LGL is characterized by a chronic, indolent clonal growth of LGL cells, leading to neutropenia and splenomegaly. As opposed to Felty syndrome, T-LGL may develop early in the course of RA. Leukopenia apart from these disorders is uncommon and most often a side effect of drug therapy. Acute myeloid leukemia, chronic lymphocytic leukemia, essential thrombocytosis, and polycythemia vera are not seen more frequently in patients with RA. Lymphoma is increased in patients with RA but is not typically similar to Felty syndrome in clinical presentation. The most common type of lymphoma diagnosed in patients with RA is diffuse large B-cell lymphoma.

VIII-24. The answer is A. *(Chap. 351)* Patients with rheumatoid arthritis (RA) must be monitored for specific comorbidities for which they are at increased risk. The most common cause of death in patients with RA is cardiovascular disease. The incidence of coronary artery disease and carotid atherosclerosis is higher in RA patients than in the general population even when controlling for traditional cardiac risk factors, such as hypertension, obesity, hypercholesterolemia, diabetes, and cigarette smoking. Large cohort studies have shown a two- to fourfold increased risk of lymphoma in RA patients compared with the general population. The most common histopathologic type of lymphoma is a diffuse large B-cell lymphoma. RA has not been associated with increased rates of colorectal cancer or other solid tumors, with the exception of lung cancer, which is slightly increased. Osteoporosis is more common in patients with RA than an age- and sex-matched population, with prevalence rates of 20–30%. The inflammatory milieu of the joint probably spills over into the rest of the body and promotes generalized bone loss by activating osteoclasts. Chronic use of glucocorticoids and disability-related immobility also contributes to osteoporosis. Men and post-menopausal women with RA have lower mean serum testosterone, luteinizing hormone, and dehydroepiandrosterone levels than control populations. It has thus been hypothesized that hypoandrogenism may play a role in the pathogenesis of RA or arise as a consequence of the chronic inflammatory response.

VIII-25. The answer is E. *(Chap. 351)* Once the disease process of rheumatoid arthritis (RA) is established, the most common joints of involvement are the wrists, metacarpophalangeal joints, and proximal interphalangeal joints. Distal interphalangeal joint involvement is rarely due to RA and more often due to coexisting osteoarthritis.

VIII-26. The answer is C. *(Chap. 351)* There is potential involvement of multiple organ systems in rheumatoid arthritis (RA). The most common pulmonary complication is pleural effusion that is typically exudative and presents with chest pain and dyspnea. RA is associated with a form of diffuse interstitial lung disease that may present with dyspnea and bilateral interstitial infiltrates that may be so extensive as to develop into a honeycomb pattern. Pulmonary nodules associated with RA may be solitary or multiple. They often occur in conjunction with cutaneous nodules. Bronchiectasis and respiratory bronchiolitis may also be due to RA. Many of these manifestations respond to immunosuppressive therapy. Lobar infiltrate has not been described to be caused by RA and is more commonly caused by an acute infectious etiology, often as a complication of RA immunosuppressive therapy.

VIII-27. The answer is A. *(Chap. 351)* Joint imaging is a critical tool for both diagnosis and monitoring of disease status in rheumatoid arthritis (RA). Plain radiographs, because of their ready availability and ease of film comparison, are most commonly ordered. The earliest clinical sign of RA is juxta-articular osteopenia, although this may be difficult to appreciate on newer, digitized films. Other findings include soft tissue swelling, symmetric joint space loss, and subchondral erosions most frequently in the wrists, metacarpophalangeal and proximal interphalangeal joints, and metatarsophalangeal joints.

VIII-28. The answer is D. *(Chap. 351)* The therapy of rheumatoid arthritis (RA) has changed dramatically in the last two decades with the development of drugs that modify the disease course of RA. Methotrexate is the disease-modifying antirheumatic drug (DMARD) of first choice for treatment of early RA. Other conventional DMARDs include hydroxychloroquine, sulfasalazine, and leflunomide. Leflunomide, an inhibitor of pyrimidine synthesis, is efficacious as a single agent or in combination with methotrexate. Hydroxychloroquine and sulfasalazine are typically reserved for mild disease. The biologic DMARDs have dramatically improved the treatment of RA in the last decade. There are currently five anti–tumor necrosis factor agents, including infliximab, approved for use in patients with RA. Rituximab, an anti-CD20 antibody, is approved for refractory RA in combination with methotrexate. It is more efficacious in seropositive than seronegative patients. Other biologics approved for use in RA include anakinra (interleukin [IL]-1 receptor antagonist), abatacept (CD28/CD80/86 antagonist), and tocilizumab (IL-6 antagonist). Nonsteroidal anti-inflammatory drugs, including naproxen, were formerly used as core RA therapy. However, they are now used as adjunctive treatment for symptom management. They are not considered DMARDs.

VIII-29. The answer is D. *(Chap. 352)* Acute rheumatic fever is almost universally due to group A streptococcal disease in present time, although virtually all streptococcal disease may be capable of precipitating rheumatic fever. Although skin infections may be associated with rheumatic fever, far and away the most common presentation is with preceding pharyngitis. There is a latent period of approximately 3 weeks from an episode of sore throat to presentation of acute rheumatic fever. The most common manifestations are fever and polyarthritis, with polyarthritis present in 60–75% of cases. Carditis may also be present, although somewhat less frequently (50–60% of cases). Chorea and indolent carditis may have a subacute presentation. Chorea is present in 2–30% of affected individuals, whereas erythema marginatum and subcutaneous nodules are rare. Sixty percent of patients with acute rheumatic fever progress to rheumatic heart disease with the endocardium, pericardium, and myocardium all potentially involved. All patients with acute rheumatic fever should receive antibiotics sufficient to treat the precipitating group A streptococcal infection.

VIII-30. The answer is D. *(Chap. 352)* This patient has a history suggestive of recurrent bouts of acute rheumatic fever (ARF) with evidence of mitral regurgitation, mitral stenosis, and aortic regurgitation on physical examination. This and the presence of atrial fibrillation imply severe rheumatic heart disease. Risk factors for this condition include poverty and crowded living conditions. As a result, ARF is considerably more common in the developing world. Daily aspirin is the treatment of choice for the migratory large-joint arthritis and fever that are common manifestations of ARF. Practitioners sometimes use steroids during acute bouts of carditis to quell inflammation, although this remains a controversial practice and has no role between flares of ARF. Secondary prophylaxis with either daily oral penicillin or, preferably, monthly IM injections is considered the best method to prevent further episodes of ARF and, therefore, prevent further valvular damage. Primary prophylaxis with penicillin on an as-needed basis is equally effective for preventing further bouts of carditis. However, most episodes of sore throat are too minor for patients to present to a physician. Therefore, secondary prophylaxis is considered preferable in patients who already have severe valvular disease. Doxycycline is not a first-line agent for group A *Streptococcus*, the pathogen that incites ARF.

VIII-31. The answer is A. *(Chap. 352)* There is a latent period of approximately 3 weeks (1–5 weeks) between the precipitating group A streptococcal infection and the appearance of the clinical features of acute rheumatic fever (ARF). The exceptions are chorea and indolent carditis, which may follow prolonged latent periods lasting up to 6 months. Although many patients report a prior sore throat, the preceding group A streptococcal infection is commonly subclinical; in these cases, it can only be confirmed using streptococcal antibody testing. The most common clinical features are polyarthritis (present in 60–75% of cases) and carditis (50–60%). The prevalence of chorea in ARF varies substantially between populations, ranging from <2 to 30%. Erythema marginatum and subcutaneous nodules are now rare, being found in <5% of cases.

VIII-32. The answer is E. *(Chap. 353)* Involvement of the gastrointestinal tract, which can affect any level, occurs in up to 90% of scleroderma patients with both limited and diffuse

TABLE VIII-32 Prominent Gastrointestinal Manifestations of Systemic Sclerosis and Their Management

Site	Principal Manifestation	Management
Oropharynx	Diminished oral aperture Dry mouth Periodontitis, gingivitis swallowing	Periodontal care Artificial saliva Swallowing therapy
Esophagus	Reflux Dysphagia Strictures Barret metaplasia	Lifestyle modifications Prokinetic drugs proton pump inhibitors Endoscopic procedures
Stomach	Gastroparesis Gastric antral vascular ectasia (watermelon stomach)	Prokinetic agents Endoscopic laser cryotherapy
Small and large intestines	Bacterial overgrowth Diarrhea/constipation Pseudo-obstruction Pneumatosis intestinalis Malabsorption Colonic pseudodiverticula	Laxatives Prokinetic agents Rotating antibiotics Octreotide Parenteral nutritional support
Anorectum	Sphincter incompetence	Biofeedback, sacral nerve stimulation, surgery

cutaneous disease (Table VIII-32). All of the gastrointestinal conditions above can occur in association with scleroderma, but impaired intestinal motility and small bowel bacterial overgrowth are the conditions that typically result in diarrhea, bloating, and weight loss. Patients with gastroesophageal reflux disease typically have symptoms like heartburn, regurgitation, and dysphagia. Gastric antral vascular ectasia (GAVE) in the antrum may also occur. These subepithelial lesions, reflecting the diffuse small-vessel vasculopathy of systemic sclerosis, are described as "watermelon stomach" due to their endoscopic appearance. Patients with GAVE present with recurrent episodes of gastrointestinal bleeding, resulting in chronic unexplained anemia.

VIII-33. **The answer is A.** *(Chap. 353)* Raynaud phenomenon, the most frequent extracutaneous complication of systemic sclerosis (SSc), is characterized by episodes of reversible vasoconstriction in the fingers and toes, sometimes also affecting the tip of the nose and earlobes. Raynaud's phenomenon in scleroderma can be associated with ischemic digital ulcers and loss of digits. Although it is often silent, variable cardiac involvement in SSc is detected in 10–50% of patients screened with sensitive diagnostic tools. Clinical cardiac involvement, more frequent in diffuse cutaneous SSc than in limited cutaneous SSc, may be primary or secondary to pulmonary arterial hypertension (PAH), interstitial lung disease, or renal involvement, and is associated with poor outcomes. The endocardium, myocardium, and pericardium may each be affected separately or together. Pericardial involvement is manifested as pericarditis, pericardial effusions, constrictive pericarditis, and rarely, cardiac tamponade. Conduction system fibrosis occurs commonly and may be silent or manifested by heart block. Microvascular involvement, recurrent vasospasm, and ischemia-reperfusion injury contribute to patchy myocardial fibrosis, resulting in asymptomatic systolic or diastolic left ventricular dysfunction that may progress to overt heart failure. Acute or subacute myocarditis leading to left ventricular dysfunction may occur, and diagnosis requires cardiac MRI or endomyocardial biopsy. While conventional echocardiography has low sensitivity for detecting preclinical heart involvement in SSc, newer modalities such as tissue Doppler echocardiography, cardiac MRI, and nuclear imaging (single photon emission CT) reveal a high prevalence of abnormal myocardial function or perfusion. The serum levels of N-terminal pro-brain natriuretic peptide, a ventricular hormone elevated in SSc-PAH, may also have utility as markers of primary cardiac involvement. Aortic aneurysms have not been reported as increased in patients with scleroderma.

VIII-34. **The answer is A.** *(Chap. 353)* The prognosis for patients with scleroderma renal disease is poor. In scleroderma renal crisis patients, prompt treatment with an angiotensin-converting enzyme (ACE) inhibitor may reverse acute renal failure. In recent studies, the initiation of ACE inhibitor therapy resulted in 61% of patients having some degree of renal recovery and not needing chronic dialysis support. The survival rate is estimated to be 80–85% at 8 years. Among patients who needed dialysis, when treated with ACE inhibitors, over 50% were able to discontinue dialysis after 3 to 18 months. Therefore, ACE inhibitors should be used even if the patient requires dialysis support.

VIII-35. The answer is C. *(Chap. 353)* Virtually every organ can be clinically affected with cutaneous systemic sclerosis (SSc). Most patients with SSc can be classified as either limited cutaneous (lcSSc) or diffuse cutaneous (dcSSc). Although stratification of SSc patients into diffuse and limited cutaneous subsets is useful, disease expression is far more complex, and several distinct endophenotypes exist within each subset. In general, pulmonary parenchymal involvement is more common in patients with dcSSc than lcSSc.

VIII-36. The answer is A. *(Chap. 354)* The differential diagnosis for parotid gland enlargement is wide and includes infections, endocrine disorders, metabolic disorders, and other inflammatory conditions. HIV infection can cause sicca syndrome and parotid enlargement, particularly in young males as is described in this case. Primary Sjögren syndrome is more common in women, and patients often have Ro/SS-A antibodies and/or La/SS-B antibodies (Table VIII-36A and B). The patient also lacked ocular symptoms. which would be atypical for primary Sjögren syndrome. The patient had no joint complaints to suggest rheumatoid arthritis (RA). RA, like primary Sjögren syndrome, is more common in middle-aged women. Sarcoidosis can affect patients of a variety of ages and both sexes, but nothing in the case suggested any other organ involvement such as pulmonary, skin, or joint involvement. IgG4 syndrome typically occurs in middle-aged to elderly men and can affect a wide range of organs *(Chap. 361)*.

VIII-37. The answer is D. *(Chap. 354)* The patient presented with classic symptoms for primary Sjögren syndrome including dry mouth and eyes. This condition may be primary, as in this case, or secondary in association with another connective tissue disease such as scleroderma or rheumatoid arthritis. Many autoantibodies may be demonstrated in the serum of patients with Sjögren syndrome, including antibodies to Ro/SS-A or La/SS-B. Sialometry will demonstrate decreased production of saliva and MRI or magnetic resonance sialography of the major salivary glands may also demonstrate abnormalities. Ocular involvement with decreased tear production is demonstrated by the Schirmer I test. Scl-70 antibody is associated with scleroderma and should not be positive in primary Sjögren syndrome.

TABLE VIII-36A Subsets of Systemic Sclerosis (SSc): Features of Limited Cutaneous SSc versus Diffuse Cutaneous Disease

Characteristic Feature	Limited Cutaneous SSc	Diffuse Cutaneous SSc
Skin involvement	Indolent onset; limited to fingers, distal to elbows, face; slow progression	Rapid onset; diffuse: fingers, extremities, face, trunk; rapid progression
Raynaud phenomenon	Antedates skin involvement, sometimes by years; may be associated with critical ischemia in the digits	Onset coincident with skin involvement; critical ischemia less common
Musculoskeletal	Mild arthralgia	Severe arthralgia, carpal tunnel syndrome, tendon friction rubs; small and large joint contractures
Interstitial lung disease	Slowly progressive, generally mild	Frequent, early onset and progression, can be severe
Pulmonary arterial hypertension	Frequent, late, may occur as an isolated complication	Often occurs in association with interstitial lung disease
Scleroderma renal crisis	Very rare	Occurs in 15%; onset may be fulminant; generally early (<4 years from disease onset)
Calcinosis cutis	Frequent, prominent	Less common, mild
Characteristic autoantibodies	Anti-centromere	Anti–topoisomerase I (Scl-70), anti-RNA polymerase III

TABLE VIII-36B **Major Systemic Sclerosis–Specific Autoantibodies and Principal Associated Features**

Target Antigen	SSc Subset	Prominent Characteristic Clinical Association
DNA Topoisomerase I (Scl-70) Speckled pattern	dcSSc	Tendon friction rubs, digital ischemic ulcers, scleroderma, extensive skin involvement, early ILD, cardiac involvement, scleroderma renal crisis
Centromere proteins Discreet speckled (centromere) pattern	lcSSc	Digital ischemic ulcers, calcinosis cutis, isolated PAH; renal crisis rare
RNA polymerase III Speckled pattern	dcSSc	Rapidly progressive skin, tendon friction rubs, joint contractures, GAVE, renal crisis, contemporaneous cancers; digital ulcers rare
U3-RNP (fibrillarin) Nucleolar pattern	dc/lcSSc	PAH, ILD, scleroderma renal crisis, GI tract involvement, myositis
Th/T_0 Nucleolar pattern	lcSSc	ILD, PAH
PM/Scl Nucleolar pattern	lcSSc	Calcinosis cutis, ILD, myositis overlap
Ku Speckled pattern	Overlap	SLE, myositis overlap
U1-RNP Speckled pattern	MCTD	PAH, inflammatory arthritis, myositis overlap
U11/U12 RNP Speckled pattern	dc/lcSSc	ILD

Abbreviations: dcSSc, diffuse cutaneous SSc; GAVE, gastric antral vascular ectasia; GI, gastrointestinal; ILD, interstitial lung disease; lcSSc, limited cutaneous SSc; MCTD, mixed connective tissue disease; PAH, pulmonary arterial hypertension; SLE, systemic lupus erythematosus.

VIII-38. **The answer is D.** *(Chap. 354)* Lymphoma is well known to develop specifically in the late stage of Sjögren syndrome. Common manifestations of this malignant condition include persistent parotid gland enlargement, purpura, leukopenia, cryoglobulinemia, and low C4 complement levels. Most of the lymphomas are extranodal, marginal zone B cell, and low grade. Low-grade lymphomas may be detected incidentally during a labial biopsy. Mortality is higher in patients with concurrent B symptoms (fevers, night sweats, and weight loss), a lymph node mass >7 cm, and a high or intermediate histologic grade.

VIII-39. **The answer is A.** *(Chap. 383)* Although Sjögren syndrome most commonly affects the eyes and mouth, there are a number of common extraglandular sites of involvement. The most common is arthritis or arthralgias that complicate up to 60% of cases. Raynaud phenomenon is the second most common extraglandular site. Lung involvement and vasculitis are found in less than 20% of patients. Lymphoma, although a concerning and highly morbid complication, is relatively rare, affecting only 6% of Sjögren patients.

VIII-40. **The answer is C.** *(Chap. 355)* Ideally, coordinated therapy is directed at both the skin and joints in psoriatic arthritis (PsA). Use of the anti–tumor necrosis factor-α agents has revolutionized the treatment of PsA. Prompt and dramatic resolution of both arthritis and skin lesions has been observed in large, randomized controlled trials. Many of the responding patients had long-standing disease that was resistant to all previous therapy, as well as extensive skin disease. The anti–IL-17A monoclonal antibody secukinumab is effective in treating both psoriasis and PsA. Ixekizumab, another IL-17 antagonist, is approved for treatment of psoriasis and PsA. Ustekinumab, a monoclonal antibody to the shared IL-23/IL-12p40 subunit, is an efficacious treatment for psoriasis and has some efficacy for PsA. Other treatment for PsA has been based on drugs that have efficacy in rheumatoid arthritis (RA) and/or in psoriasis. Methotrexate in doses of 15–25 mg/wk has moderate efficacy for psoriasis, but limited efficacy for PsA. Sulfasalazine (usually given in doses of 2–3 g/d) may not have efficacy for either, and neither regimen halts progression of erosive joint disease. Other agents with efficacy in psoriasis reported to benefit PsA are cyclosporine, retinoic acid derivatives, and psoralens plus ultraviolet A light. The pyrimidine synthetase inhibitor leflunomide has been shown to be beneficial in PsA, with modest benefit for psoriasis. Rituximab is approved by the U.S. Food and Drug Administration for RA but has not shown efficacy in psoriasis or psoriatic arthritis. Rituximab is more effective in patients with RA and autoantibodies (rheumatoid factor and anti–cyclic citrullinated protein), which are not seen in most patients with psoriatic arthritis.

VIII-41. **The answer is B.** *(Chap. 355)* Many patients present with some features of one or more of the spondyloarthritides. Until recently, these patients were said to have *undifferentiated spondyloarthritis (SpA)*, or simply *spondyloarthritis*, as defined by the 1991 European Spondyloarthropathy Study Group criteria. For example, a patient may present with inflammatory synovitis of one knee, Achilles tendinitis, and dactylitis of one digit. Some of these patients may have reactive arthritis in which the triggering infection remains clinically silent. In some other cases, the patient subsequently develops inflammatory bowel disease or psoriasis. The diagnosis of undifferentiated SpA was also commonly applied to patients with inflammatory back pain who did meet modified New York criteria for ankylosing spondylitis. Comparable to the classification criteria for axial symptoms, consensus groups have formulated criteria for peripheral SpA (Table VIII-41). This is intended to exclude patients with axial symptoms and thus to divide the universe of patients with SpA into predominantly axial and predominantly peripheral subsets. This patient is seronegative for rheumatoid factor and anti–cyclic citrullinated protein spondyloarthritides as well as having dactylitis and enthesitis, suggesting against rheumatoid arthritis. There is no personal or family history of psoriasis to suggest psoriatic arthritis. She denies inflammatory back pain and has a normal sacroiliac MRI suggesting against ankylosing spondylitis.

TABLE VIII-41 Assessment of Spondyloarthritis International Society (ASAS) Criteria for Peripheral Spondyloarthritis[a]

Arthritis[b] *or* Enthesitis *or* Dactylitis

PLUS EITHER

One or more of the following SpA features:
- Psoriasis
- Crohn disease or ulcerative colitis
- Preceding infection
- Uveitis
- HLA-B27
- Sacroiliitis on imaging (radiographs or MRI)

OR two or more of the following SpA features:
- Arthritis
- Enthesitis
- Dactylitis
- Inflammatory back pain ever
- Family history for SpA

[a] Sensitivity 78%, specificity 82%.

[b] Peripheral arthritis, usually predominantly lower limb and/or asymmetric. The various spondyloarthritis (SpA) features are as defined in Table 355-1 in HPIM 20. Preceding infection refers to preceding gastrointestinal or urogenital infection.

Source: Data from Rudwaleit M et al: The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. *Ann Rheum Dis* 70:25, 2011.

VIII-42. **The answer is E.** *(Chap. 355)* The syndrome of synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) is characterized by a variety of skin and musculoskeletal manifestations. Dermatologic manifestations include palmoplantar pustulosis, acne conglobata, acne fulminans, and hidradenitis suppurativa. Plaque psoriasis is not commonly associated with SAPHO syndrome, but it can occur commonly in psoriatic arthritis. The main musculoskeletal findings are sternoclavicular and spinal hyperostosis, chronic recurrent foci of sterile osteomyelitis, and axial or peripheral arthritis. Cases with one or a few manifestations are probably the rule. The erythrocyte sedimentation rate and/or

C-reactive protein are usually mildly to moderately elevated, occasionally dramatically. In some cases, bacteria, most often *Propionibacterium acnes*, have been cultured from bone biopsy specimens and occasionally other sites. Inflammatory bowel disease was coexistent in 8% of patients in one large series. HLA-B27 is not associated. Either bone scan or CT scan is helpful diagnostically. An MRI report described characteristic vertebral body corner cortical erosions in 12 of 12 patients.

VIII-43. **The answer is D.** *(Chap. 355)* Ankylosing spondylitis is closely correlated with the presence of the histocompatibility antigen HLA-B27. In North American whites, the prevalence of B27 is 7%, but in patients with ankylosing spondylitis, it is 75–90%. Not all persons with B27 develop ankylosing spondylitis; the disease is only present in 1–6% of B27-positive individuals.

VIII-44. **The answer is A.** *(Chap. 355)* Although the most serious spine complication of ankylosing spondylitis is fracture, there are a number of important extra-articular manifestations. Anterior uveitis is the most common, occurring in 40% of patients with ankylosing spondylitis. Inflammatory bowel disease has been reported to be frequently present. Less common complications include aortic insufficiency, third-degree heart block, pulmonary nodules and upper lobe fibrosis, cardiac dysfunction, retroperitoneal fibrosis, prostatitis, and amyloidosis.

VIII-45. **The answer is E.** *(Chaps. 355)* Reactive arthritis refers to an acute, nonpurulent arthritis that occurs after an infection elsewhere in the body. Often presenting with lower joint inflammatory arthritis occurring 1–4 weeks after a diarrheal episode, reactive arthritis may also include uveitis or conjunctivitis, dactylitis, urogenital lesions, and characteristic mucocutaneous lesions such as keratoderma blennorrhagicum. The most common organisms associated with reactive arthritis are *Shigella* species, although *Yersinia*, *Chlamydia*, and, to a much lesser extent, *Salmonella* and *Campylobacter*, have been described. Although more common in children residing in developing countries, over 400,000 annual cases of *Shigella* species infections occur in the United States. These infections mostly occur in children 4–11 years old. Most U.S. cases are due to *Shigella sonnei*, with *S. flexneri* the second most common cause.

VIII-46. **The answer is C.** *(Chap. 355)* Enthesopathy or enthesitis is the term used to describe inflammation at the site of tendinous or ligamentous insertion into bone. This type of inflammation is seen most frequently in patients with seronegative spondyloarthropathies and various infections, especially viral infections. The other definitions apply to other terms used in the orthopedic and rheumatic examination. Subluxation is the alteration of joint alignment so that articulating surfaces incompletely approximate each other. Synovitis refers to inflammation at the site of tendinous or ligamentous insertion into bone. Inflammation of a saclike cavity near a joint that decreases friction is the definition of bursitis. Finally, crepitus is a palpable vibratory or crackling sensation elicited with joint motion.

VIII-47. **The answer is D.** *(Chap. 355)* Nail changes in the fingers or toes occur in up to 90% of patients with psoriatic arthritis (PsA), compared with 40% of psoriatic patients without arthritis, and pustular psoriasis is said to be associated with more severe arthritis. Several articular features distinguish PsA from other joint disorders; such hallmark features include dactylitis and enthesitis. Dactylitis occurs in >30%; enthesitis and tenosynovitis are also common and are probably present in most patients, although often not appreciated on physical examination. Shortening of digits because of underlying osteolysis is particularly characteristic of PsA, and there is a much greater tendency than in rheumatoid arthritis for both fibrous and bony ankylosis of small joints. Rapid ankylosis of one or more proximal interphalangeal (PIP) joints early in the course of disease is not uncommon. Back and neck pain and stiffness are also common in PsA. Diarrhea is not a feature of PsA.

VIII-48. **The answer is A.** *(Chap. 355)* Aortic insufficiency, sometimes leading to congestive heart failure, occurs in a small percentage of patients, occasionally early. Third-degree heart block may occur alone or together with aortic insufficiency. Subclinical pulmonary lesions and cardiac dysfunction may be relatively common.

VIII-49. The answer is A. *(Chap. 356)* This patient presents with polyarteritis nodosa related to hepatitis B. A similar syndrome has been described with hepatitis C infection. Nonspecific signs and symptoms are the hallmarks of polyarteritis nodosa (Table VIII-49). Fever, weight loss, and malaise are present in over one-half of cases. Patients usually present with vague symptoms such as weakness, malaise, headache, abdominal pain, and myalgias that can rapidly progress to a fulminant illness. Specific complaints related to the vascular involvement within a particular organ system may also dominate the presenting clinical picture as well as the entire course of the illness. There are no diagnostic serologic tests for polyarteritis nodosa. In >75% of patients, the leukocyte count is elevated with a predominance of neutrophils. The anemia of chronic disease may be seen, and an elevated erythrocyte sedimentation rate is almost always present. Other common laboratory findings reflect the particular organ involved. Hypergammaglobulinemia may be present, and all patients should be screened for hepatitis B and C. The vascular lesion in polyarteritis nodosa is a necrotizing inflammation of small- and medium-sized muscular arteries. The lesions are segmental and tend to involve bifurcations and branchings of arteries. They may spread circumferentially to involve adjacent veins. However, involvement of venules is not seen in polyarteritis nodosa and, if present, suggests the diagnosis of microscopic polyangiitis. In the acute stages of disease, polymorphonuclear neutrophils infiltrate all layers of the vessel wall and perivascular areas, which results in intimal proliferation and degeneration of the vessel wall. Mononuclear cells infiltrate the area as the lesions progress to the subacute and chronic stages. Fibrinoid necrosis of the vessels ensues with compromise of the lumen, thrombosis, infarction of the tissues supplied by the involved vessel, and, in some cases, hemorrhage. Skin biopsy in IgA vasculitis shows confirming leukocytoclastic vasculitis with IgA and C3 deposition by immunofluorescence. Interface dermatitis is seen in systemic lupus erythematosus, dermatomyositis, and with certain infections. Noncaseating granulomas are noted on skin biopsies in sarcoidosis. Septal panniculitis can be seen in erythema nodosum.

TABLE VIII-49 Clinical Manifestations Related to Organ System Involvement in Polyarteritis Nodosa

Organ System	Percentage Incidence	Clinical Manifestations
Renal	60	Renal failure, hypertension
Musculoskeletal	64	Arthritis, arthralgia, myalgia
Peripheral nervous system	51	Peripheral neuropathy, mononeuritis multiplex
Gastrointestinal tract	44	Abdominal pain, nausea and vomiting, bleeding, bowel infarction and perforation, cholecystitis, hepatic infarction, pancreatic infarction
Skin	43	Rash, purpura, nodules, cutaneous infarcts, livedo reticularis, Raynaud phenomenon
Cardiac	36	Congestive heart failure, myocardial infarction, pericarditis
Genitourinary	25	Testicular, ovarian, or epididymal pain
Central nervous system	23	Cerebral vascular accident, altered mental status, seizure

Source: Reproduced with permission from Cupps TR et al: *The Vasculitides*. Philadelphia: Saunders, 1981.

VIII-50. The answer is B. *(Chap. 356)* Takayasu arteritis is an inflammatory and stenotic disease of medium- and large-sized arteries. It is an uncommon disease with an estimated annual incidence rate of 1.2–2.6 cases per million. It is most prevalent in adolescent girls and young women. Takayasu arteritis disease involves medium- and large-sized arteries, with a strong predilection for the aortic arch and its branches; the pulmonary artery may also be involved (Table VIII-50). The involvement of the major branches of the aorta is much more marked at their origin than distally. The disease is a panarteritis with inflammatory mononuclear cell infiltrates and occasionally giant cells. There are marked intimal proliferation and fibrosis, scarring and vascularization of the media, and disruption

TABLE VIII-50 Frequency of Arteriographic Abnormalities and Potential Clinical Manifestations of Arterial Involvement in Takayasu Arteritis

Artery	Percentage of Arteriographic Abnormalities	Potential Clinical Manifestations
Subclavian	93	Arm claudication, Raynaud phenomenon
Common carotid	58	Visual changes, syncope, transient ischemic attacks, stroke
Abdominal aorta[a]	47	Abdominal pain, nausea, vomiting
Renal	38	Hypertension, renal failure
Aortic arch or root	35	Aortic insufficiency, congestive heart failure
Vertebral	35	Visual changes, dizziness
Coeliac axis[a]	18	Abdominal pain, nausea, vomiting
Superior mesenteric[a]	18	Abdominal pain, nausea, vomiting
Iliac	17	Leg claudication
Pulmonary	10–40	Atypical chest pain, dyspnea
Coronary	<10	Chest pain, myocardial infarction

[a] Arteriographic lesions at these locations are usually asymptomatic but may potentially cause these symptoms.
Source: Data from Kerr GS et al: Takayasu arteritis. *Ann Intern Med* 120:919, 1994.

and degeneration of the elastic lamina. Narrowing of the lumen occurs with or without thrombosis. The vasa vasorum are frequently involved. Pathologic changes in various organs reflect the compromise of blood flow through the involved vessels. The cerebral arteries are not commonly affected in Takayasu arteritis.

VIII-51. The answer is D. *(Chap. 356)* The patient presents with classic symptoms for granulomatosis with polyangiitis. The average age of diagnosis is 40 years and there is a male predominance. Upper respiratory symptoms often predate lung or renal findings and may even present with septal perforation. The diagnosis is made by demonstration of necrotizing granulomatous vasculitis on biopsy. Pulmonary tissue offers the highest yield. Biopsy of the upper airway usually shows the granulomatous inflammation but infrequently shows vasculitis. Renal biopsy may show the presence of pauci-immune glomerulonephritis.

VIII-52. The answer is C. *(Chap. 356)* The patient has a classic presentation for giant cell arteritis with associated polymyalgia rheumatica including headache, jaw claudication, and visual disturbances. Her age makes this diagnosis highly likely as well. The diagnosis is confirmed by temporal artery biopsy; however, in the presence of visual symptoms, initiation of therapy should not be delayed pending a biopsy because the biopsy may be positive even after approximately 14 days of glucocorticoid therapy. Delay in therapy risks irreversible visual loss. Additionally, a dramatic response to therapy may lend further support to the diagnosis. Although erythrocyte sedimentation rate is nearly universally elevated, it is not specific for the diagnosis. Temporal artery ultrasound may be suggestive but is not diagnostic.

VIII-53. The answer is C. *(Chap. 356)* The most common manifestations of cryoglobulinemic vasculitis are cutaneous vasculitis, arthritis, peripheral neuropathy, and glomerulonephritis. The demonstration of circulating cryoprecipitates is a critical component of the diagnosis, and often rheumatoid factor can be found as well. Because hepatitis C infection is present in the vast majority of patients with cryoglobulinemic vasculitis, infection should be investigated in all patients with this clinical syndrome.

VIII-54. The answer is C. *(Chap. 356)* The most likely cause of the acute coronary syndrome in this patient is thrombosis of a coronary artery aneurysm in an individual with a past history of Kawasaki disease. Kawasaki disease is an acute multisystem disease that primarily presents in children <5 years of age. The clinical manifestations in childhood are nonsuppurative cervical lymphadenitis; desquamation of the fingertips; and erythema of the oral cavity, lips, and palms. Approximately 25% of cases are associated with coronary artery aneurysms that occur late in illness in the convalescent stage. Early treatment (within 7–10 days of onset) with IV immunoglobulin and high-dose aspirin decreases the risk of developing coronary aneurysms to about 5%. Even if coronary artery aneurysms develop, most regress over the course of the first year if the size is <6 mm. Aneurysms >8 mm, however, are unlikely to regress. Complications of persistent coronary artery aneurysms include rupture, thrombosis and recanalization, and stenosis at the outflow area. Dissection of the aortic root and coronary ostia is a common cause of death in Marfan syndrome and can also be seen with aortitis due to Takayasu arteritis. In this patient, there is no history of hypertension, limb ischemia, or systemic symptoms that would suggest an active vasculitis. In addition, there are no other ischemic symptoms that would be expected in Takayasu arteritis. Myocardial bridging overlying a coronary artery is seen frequently at autopsy but is an unusual cause of ischemia. The possibility of cocaine use as a cause of myocardial ischemia in a young individual must be considered, but given the clinical history, it is a less likely cause of ischemia in this case.

VIII-55. The answer is E. *(Chap. 356)* Prior to initiation of azathioprine, thiopurine methyltransferase, an enzyme involved in the metabolism of azathioprine, should be assayed because inadequate levels may result in severe cytopenia. The antineutrophil cytoplasmic antibody (ANCA) titer can be misleading and should not be used to assess disease activity. Many patients who achieve remission continue to have elevated titers for years. Results from a large prospective study found that increases in ANCA were not associated with relapse and that only 43% of patients relapsed within 1 year of an increase in ANCA levels. Thus, a rise in ANCA by itself is not a harbinger of immediate disease relapse and should not lead to reinstitution or increase in immunosuppressive therapy.

VIII-56. The answer is C. *(Chap. 356)* Granulomatosis with polyangiitis (Wegener) is a small-vessel vasculitis that involves the lung in >80% of cases. One-third of patients with radiographic abnormalities may be asymptomatic. It typically also involves the upper respiratory tract and the kidney. Surgical biopsies of radiographically abnormal pulmonary parenchyma have a diagnostic yield of approximately 90% in patients with granulomatosis with polyangiitis (Wegener). Biopsy may also differentiate vasculitis from infection or malignancy. The yield of bronchoscopic transbronchial biopsy is substantially lower than surgical biopsy. Cryoglobulinemic vasculitis and IgA vasculitis (Henoch-Schönlein) are small-vessel vasculitides that typically involve the skin and kidney. Polyarteritis nodosa is a medium-vessel vasculitis that typically involves the mesenteric vessels. Cutaneous vasculitis represents the most common vasculitic feature and can be seen in a broad spectrum of settings including infections, medications, malignancies, and connective tissue diseases.

VIII-57. The answer is E. *(Chap. 357)* Behçet syndrome is a multisystem disorder presenting with recurrent oral and genital ulcerations as well as ocular, skin, and joint involvement. The diagnosis is clinical and based on internationally agreed diagnostic criteria. Recurrent oral aphthous ulcerations are a sine qua non for the diagnosis of Behçet syndrome. The ulcers are usually painful, shallow, or deep with a central yellowish necrotic base, appear singly or in crops, and can be located anywhere in the oral cavity. Genital ulcers are less common but more specific, are painful, do not affect the glans penis or urethra, and produce scrotal and vulvar scars. Skin involvement is observed in 80% of patients and includes folliculitis, erythema nodosum, acne-like rashes, and, infrequently, vasculitis, Sweet syndrome, and pyoderma gangrenosum. Nonspecific skin inflammatory reactivity to scratch or intradermal saline injection (pathergy test) is a specific manifestation. Nondeforming arthritis or arthralgias are seen in 50% of patients and affect mostly the knees and ankles. Enthesopathy, avascular necrosis, myalgia, and myositis can be also seen. Superficial or deep peripheral vein thrombosis is seen in 30% of patients. Pulmonary emboli are a rare complication. Eye involvement with scarring and bilateral panuveitis is the most dreaded complication, since it occasionally progresses rapidly to blindness. Uveitis occurs in 10–15% of patients, primarily in males. It is usually present at the onset but may also develop within the first few years. In addition to iritis, posterior uveitis, retinal vessel occlusions, and optic neuritis can be rarely seen in some patients. Scleritis, a complication of rheumatoid arthritis, is not commonly reported in association with Behçet syndrome.

VIII-58. **The answer is C.** *(Chap. 357)* Behçet syndrome is diagnosed clinically. Recurrent oral ulceration is required for the diagnosis. The ulcers may be single or multiple, are shallow based with a yellow necrotic base, and are painful. They are generally small, <10 mm in diameter. In addition, the diagnosis of Behçet syndrome requires two of the following: recurrent genital ulceration, eye lesions, skin lesions, and pathergy test. Nonspecific skin inflammatory reactivity to any scratches or intradermal saline injection (pathergy test) is common and specific.

VIII-59. **The answer is A.** *(Chap. 357)* Behçet syndrome is a multisystem disorder of uncertain cause that is marked by oral and genital ulcerations and ocular involvement. This disorder affects males and females equally and is more common in persons of Mediterranean, Middle Eastern, and Far Eastern descent. Approximately 50% of these persons have circulating autoantibodies to human oral mucosa. The clinical features are quite varied. The presence of recurrent aphthous ulcerations is essential for the diagnosis. Most of these patients have primarily oral ulcerations, although genital ulcerations are more specific for the diagnosis. The ulcers are generally painful, can be shallow or deep, and last for 1 or 2 weeks. Other skin involvement may occur, including folliculitis, erythema nodosum, and vasculitis. Eye involvement is the most dreaded complication because it may progress rapidly to blindness. It often presents as panuveitis, iritis, retinal vessel occlusion, or optic neuritis. This patient also presents deep venous thrombosis, which is present in 25–33% of these patients. Neurologic involvement occurs in up to 10%. Laboratory findings are nonspecific with elevations in the erythrocyte sedimentation rate and the white blood cell count. Bullous pemphigoid is a polymorphic autoimmune subepidermal blistering disease usually seen in the elderly. Initial lesions may consist of urticarial plaques; most patients eventually display tense blisters on either normal-appearing or erythematous skin. The lesions are usually distributed over the lower abdomen, groin, and flexor surface of the extremities; oral mucosal lesions are found in some patients. Discoid lupus erythematosus is the cutaneous form of systemic lupus erythematosus and is characterized by atrophic, depigmented plaques and patches surrounded by hyperpigmentation and erythema in association with scarring and alopecia.

VIII-60. **The answer is D.** *(Chap. 358)* This patient likely has inclusion body myositis (IBM). IBM usually manifests in patients over the age of 50 years and is slightly more common in men than women. It is associated with slowly progressive weakness and muscle atrophy that has a predilection for early involvement of the wrist and finger flexors in the arms and quadriceps in the legs (Figure VIII-60). Creatinine kinase levels can be normal or only slightly elevated (usually <10 times normal). Muscle biopsies demonstrate endomysial inflammatory infiltrates predominantly composed of CD8+ T cells and macrophages surrounding and invading non-necrotic muscle fibers, major histocompatibility complex 1 expression on the sarcolemma, fibers with rimmed vacuoles, cytochrome oxidase negative fibers, and inclusions on light or electron microscopy. The inclusions contain β-sheet misfolded proteins (amyloid), but they are difficult to appreciate with routine Congo red stain (they are seen on frozen but not paraffin sections). In dermatomyositis, perifascicular atrophy and perivascular inflammation are appreciated. Multifocal necrotic and regenerating muscle fibers with a paucity of inflammation is seen in immune-mediated necrotizing myopathy. In chronic glucocorticoid-related myopathy, type 2 muscle fiber atrophy will be seen on the biopsy.

VIII-61. **The answer is E.** *(Chap. 358)* Dermatomyositis, polymyositis, antisynthetase syndrome, and immune-mediated necrotizing myopathy (IMNM) are typically responsive to immunotherapy (Table VIII-61). High-dose glucocorticoids (i.e., starting dose of prednisone 0.75–1.0 mg/kg per day) is considered the first-line treatment. There is uncertainty regarding when to start second-line agents (e.g., methotrexate, azathioprine, mycophenolate, Ig, or rituximab). The clinician must weigh with the patient the increased risks of immunosuppression versus possible benefits (e.g., faster improvement, steroid-sparing effect, and/or avoidance of the morbidities associated with long-term glucocorticoid use). Many start a second-line agent (usually methotrexate) with glucocorticoids in patients with severe weakness or other organ system involvement

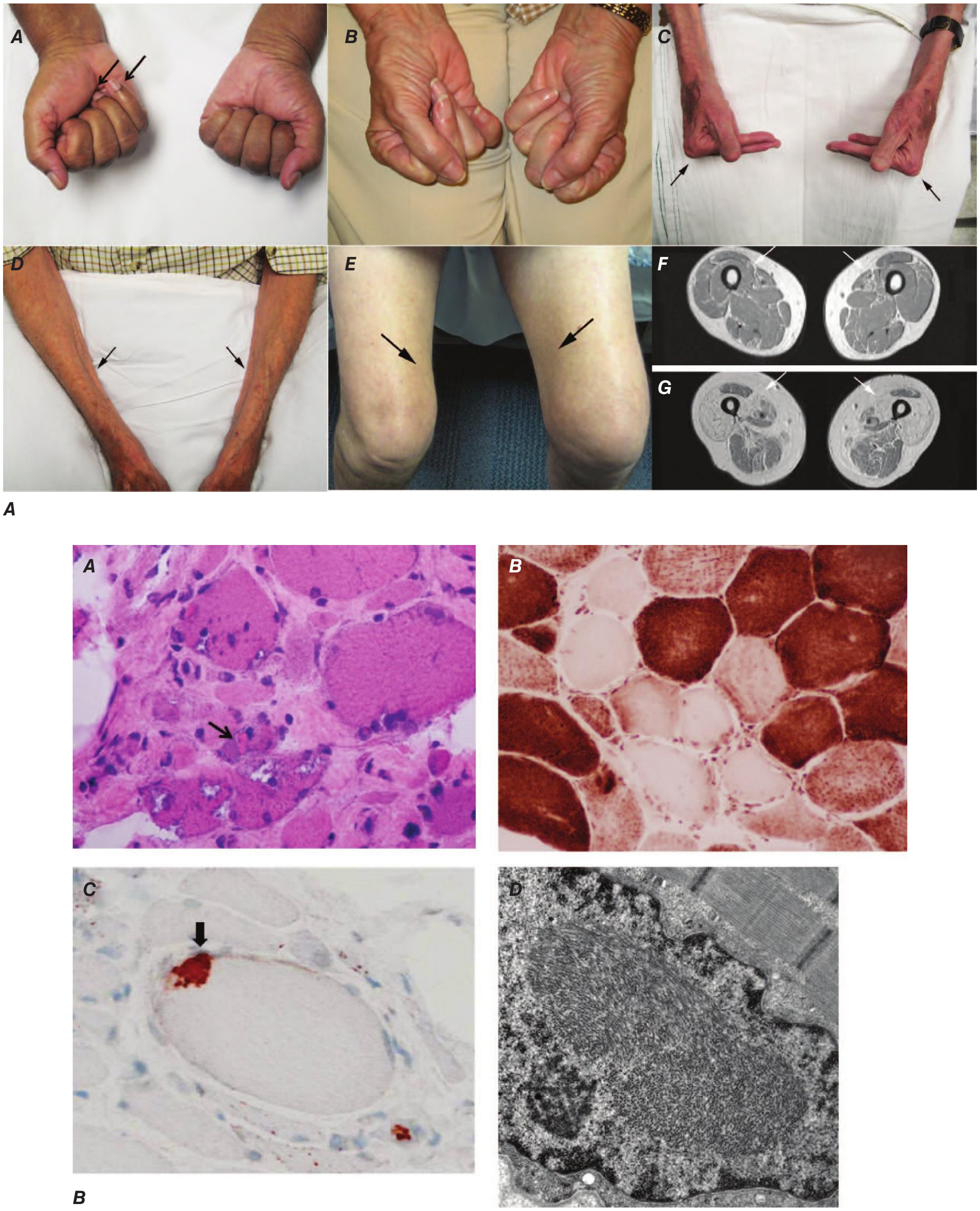


FIGURE VIII-60 **A.** Muscle manifestations of inclusion body myositis (*A–C*). Finger flexor weakness can be (***A***) subtle and multifocal (*black arrows*), (***B***) moderate, or (***C***) severe. Note even with complete paralysis of deep and superficial finger flexors, metacarpophalangeal joint flexion (*arrows*) is often maintained due to preservation of lumbricals. (***D***) Ventral forearm atrophy (*arrows*). (***E***) Atrophy of medial thighs due to loss of vastus medialis (*arrows*). (***F***) Early inclusion body myositis (IBM), with relatively preserved vastus medialis (*arrows*), in contrast to (***G***) advanced IBM with marked fibrous replacement of vastus medialis (*arrows*). **B.** Pathology of inclusion body myositis. (***A***) Scattered muscle fibers with rimmed vacuoles and rare fibers with eosinophilic inclusions (*arrow*), H&E stain. (***B***) Cytochrome oxidase stain demonstrates an increased number of pale staining or cytochrome oxidase negative muscle fibers. (***C***) Cytoplasmic inclusions stain positive with p62 within a muscle fiber (*thick arrow*). (***D***) Electron microscopy reveals 15- to 21-nm tubulofilamentous inclusions within a myonucleus.

(e.g., myocarditis, interstitial lung disease), those with increased risk of steroid complications (e.g., diabetics, osteoporosis, or post-menopausal women), and patients with IMNM who are known to have difficult to treat myositis. In patients treated initially with prednisone alone, a second-line agent is added in patients who fail to significantly improve after 2–4 months or in those who cannot be tapered to a low dose of prednisone. Most patients with IMNM do not respond to prednisone alone or even

TABLE VIII-61 Immunotherapies for Inflammatory Myopathies

Therapy	Route	Dose	Side Effects	Monitor
Prednisone	Oral	0.75–1.5 mg kg/d to start	Hypertension, fluid and weight gain, hyperglycemia, hypokalemia, cataracts, gastric irritation, osteoporosis, infection, aseptic femoral necrosis	Weight, blood pressure, serum glucose/potassium, cataract formation
Methylprednisone	IV	1 g in 100 mL/normal saline over 1–2 h, daily or every other day for 3–6 doses	Arrhythmia, flushing, dysgeusia, anxiety, insomnia, fluid and weight gain, hyperglycemia, hypokalemia, infection	Heart rate, blood pressure, serum glucose/potassium
Azathioprine	Oral	2–3 mg/kg per day; single a.m. dose	Flulike illness, hepatotoxicity, pancreatitis, leukopenia, macrocytosis, neoplasia, infection, teratogenicity	Blood count, liver enzymes
Methotrexate	Oral	7.5–20 mg weekly, single or divided doses; one day a week dosing	Hepatotoxicity, pulmonary fibrosis, infection, neoplasia, infertility, leukopenia, alopecia, gastric irritation, stomatitis, teratogenicity	Liver enzymes, blood count
	Subcutaneously	20–50 mg weekly; one day a week dosing	Same as oral	Same as PO
Cyclophosphamide	Oral IV	1.5–2 mg/kg per day; single a.m. dose 0.5 to 1.0 g/m^2 per month × 6–12 months	Bone marrow suppression, infertility, hemorrhagic cystitis, alopecia, infections, neoplasia, teratogenicity	Blood count, urinalysis
Cyclosporine	Oral	4–6 mg/kg per day, split into two daily doses	Nephrotoxicity, hypertension, infection, hepatotoxicity, hirsutism, tremor, gum hyperplasia, teratogenicity	Blood pressure, creatinine/BUN, liver enzymes, cyclosporine levels
Tacrolimus	Oral	0.1–0.2 mg/kg per d in two divided doses	Nephrotoxicity, hypertension, infection, hepatotoxicity, hirsutism, tremor, gum hyperplasia, teratogenicity	Blood pressure, creatinine/BUN, liver enzymes, tacrolimus levels
Mycophenolate mofetil	Oral	Adults (1 g BID to 1.5 g bid) Children (600 mg/m^2 per dose bid) (no >1 g/d in patients with renal failure)	Bone marrow suppression, hypertension, tremor, diarrhea, nausea, vomiting, headache, sinusitis, confusion, amblyopia, cough, teratogenicity, infection, neoplasia	Blood count
IVIg	IV	2 g/kg over 2–5 days; then 1 g/kg every 4–8 weeks as needed	Hypotension, arrhythmia, diaphoresis, flushing, nephrotoxicity, headache, aseptic meningitis, anaphylaxis, stroke	Heart rate, blood pressure, creatinine/BUN
Rituximab	IV	A course is typically 750 mg/m^2 (up to 1 g) and repeated in 2 weeks Courses are then repeated usually every 6–18 months	Infusion reactions (as per IVIg), infection, progressive multifocal leukoencephalopathy	Some check B-cell count prior to subsequent courses (but this may not be warranted)

Abbreviations: bid, twice a day; BUN, blood urea nitrogen; IVIg, intravenous immunoglobulin; m^2, body surface area; PO, by mouth.
Source: Modified with permission from Amato AA et al: *Neuromuscular Disorders*, 2nd ed. New York: McGraw Hill, 2016.

prednisone plus a second-line agent in combination. Many require triple therapy with prednisone, methotrexate, and IVIg, and if this fails, rituximab. Recent reports suggest that anti-HMGCR myopathy may respond to monotherapy with IVIg, and a large multicenter clinical trial to test this approach is currently being organized. Secukinumab is an interleukin-17A inhibitor used for psoriasis and psoriatic arthritis, not polymyositis.

VIII-62. The answer is C. *(Chap. 358)* Various autoantibodies against nuclear antigens and cytoplasmic antigens are found in up to 20% of patients with inflammatory myopathies. The antibodies to cytoplasmic antigens are directed against ribonucleoproteins involved in protein synthesis (antisynthetases) or translational transport (anti–signal-recognition particles). The antibody directed against the histidyl-transfer RNA synthetase, called anti-Jo-1, accounts for 75% of all the antisynthetases and is clinically useful because up to 80% of patients with this autoantibody will have interstitial lung disease. Patients with anti-Jo-1 may also have Raynaud phenomenon, nonerosive arthritis, and the major histocompatibility complex molecules DR3 and DRw52. Interstitial lung disease associated with anti-Jo-1 is often rapidly progressive and fatal, even if treated aggressively with cyclophosphamide or other immunosuppressants.

VIII-63. **The answer is A.** *(Chap. 358)* Dermatomyositis is associated with malignancy in up to 15% of cases; thus, age-appropriate cancer screening is indicated when this diagnosis is made. Exhaustive cancer searches are not recommended, however. Dermatomyositis may be associated occasionally with scleroderma and mixed connective tissue disease, but less frequently with systemic lupus erythematosus, rheumatoid arthritis, or Sjögren syndrome, which are more closely associated with polymyositis or inclusion body myositis (IBM). Viruses may be associated with IBM and polymyositis but are not proven to be associated with dermatomyositis. Parasites and bacteria such as cestodes and nematodes are associated with polymyositis, but not other forms of inflammatory myopathy. Finally, thyroid-stimulating immunoglobulins are not known to be associated with dermatomyositis.

VIII-64. **The answer is A.** *(Chap. 358)* Mild statin-induced myopathy is noninflammatory and usually resolves with discontinuation of therapy. In rare patients, however, muscle weakness continues to progress even after the statin is withdrawn; in these cases, a diagnostic muscle biopsy is indicated and a search for antibodies to 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) is suggested; if histologic evidence of polymyositis or necrotizing myositis is present, immunotherapy should be initiated. Antinuclear antibodies may be present but they are nonspecific in these cases. Anti-Jo-1 antibodies are associated with the antisynthetase syndromes where myositis is usually accompanied by interstitial lung disease and stereotypical skin changes. Antibodies against the signal recognition particle are not associated with statin-induced myopathy.

VIII-65. **The answer is E.** *(Chap. 358)* Relapsing polychondritis is an uncommon disorder of unknown cause characterized by inflammation of cartilage predominantly affecting the ears, nose, and laryngotracheobronchial tree. Other manifestations include scleritis, neurosensory hearing loss, polyarthritis, cardiac abnormalities, skin lesions, and glomerulonephritis. Approximately 30% of patients with relapsing polychondritis will have another rheumatologic disorder, the most frequent being systemic vasculitis such as granulomatosis with polyangiitis, followed by rheumatoid arthritis, and systemic lupus erythematosus (Table VIII-65). Nonrheumatic disorders have also been associated with relapsing polychondritis.

VIII-66. **The answer is E.** *(Chap. 359)* Relapsing polychondritis most often presents with recurrent painful swelling of the ear. Although other cartilaginous sites may be involved such as the nose and the tracheobronchial tree, these are less frequent. Episodes of ear involvement may result in floppy ears. Typically the pinna is affected while the earlobe is spared because there is no cartilage in the lobe. Cogan syndrome is a rare vasculitis syndrome involving hearing loss, but cartilage inflammation is not a feature. In this patient, recurrent trauma or irritation is a consideration but the history is not suggestive, and it would less likely be bilateral and accompanied by inflammatory findings and a relatively spared earlobe.

VIII-67. **The answer is E.** *(Chap. 360)* Sarcoid cardiac disease, which usually presents as either congestive heart failure or cardiac arrhythmias, results from infiltration of the heart muscle or conduction system by granulomas. Diffuse granulomatous involvement of the heart muscle can lead to profound cardiac dysfunction with left ventricular ejection fraction <10%. Even in this situation, improvement in the ejection fraction can occur with systemic therapy. Arrhythmias can also occur with diffuse infiltration or with more patchy

TABLE VIII-65 Disorders Associated with Relapsing Polychondritis[a]

Systemic vasculitis
Rheumatoid arthritis
Systemic lupus erythematosus
Overlapping connective tissue disease
Spondyloarthritides
Behçet syndrome
Polymyalgia rheumatica
Primary biliary cirrhosis
Pulmonary fibrosis
Hashimoto thyroiditis
Graves disease
Crohn disease
Ulcerative colitis
Myelodysplastic syndrome

[a] Systemic vasculitis is the most common association, followed by rheumatoid arthritis and systemic lupus erythematosus.

Source: Modified with permission from Michet CJ et al: Relapsing polychondritis. Survival and predictive role of early disease manifestations. *Ann Intern Med* 104:74, 1986.

cardiac involvement. If the atrioventricular node is infiltrated, heart block can occur, which can be detected by routine electrocardiography. Ventricular arrhythmias and sudden death due to ventricular tachycardia are common causes of death. Arrhythmias are best detected using 24-hour ambulatory monitoring, and electrophysiology studies may be negative. Other screening tests for cardiac disease include routine electrocardiography and echocardiography. Granulomatosis infiltration of blood vessels, including the coronary arteries or aorta, is not characteristic of sarcoidosis.

VIII-68. **The answer is E.** *(Chap. 360)* Skin involvement is eventually identified in over a third of patients with sarcoidosis. The classic cutaneous lesions include erythema nodosum, maculopapular lesions, hyperpigmentation and hypopigmentation, keloid formation, and subcutaneous nodules. A specific complex of involvement of the bridge of the nose, the area beneath the eyes, and the cheeks is referred to as *lupus pernio* and is diagnostic for a chronic form of sarcoidosis. In contrast, erythema nodosum is a transient rash that can be seen in association with hilar adenopathy and uveitis (Löfgren syndrome). Erythema nodosum is more common in women and in certain self-described demographic groups including whites and Puerto Ricans. In the United States, the other manifestations of skin sarcoidosis, especially lupus pernio, are more common in African Americans than whites. The maculopapular lesions from sarcoidosis are the most common chronic form of the disease. These are often overlooked by the patient and physician because they are chronic and not painful. Initially, these lesions are usually purplish papules and are often indurated. They can become confluent and infiltrate large areas of the skin. With treatment, the color and induration may fade. Because these lesions are caused by noncaseating granulomas, the diagnosis of sarcoidosis can be readily made by a skin biopsy. Acute cutaneous lupus can affect the face but is not nodular and often takes a malar distribution sparing the nasolabial nodes. Acne vulgaris is most common in adolescents and young adults and typically includes inflammatory pustules not seen here.

VIII-69. **The answer is E.** *(Chap. 360)* Despite multiple investigations, the cause of sarcoidosis remains unknown. Currently, the most likely etiology is an infectious or noninfectious environmental agent that triggers an inflammatory response in a genetically susceptible host. Among the possible infectious agents, careful studies have shown a much higher incidence of *Propionibacterium acnes* in the lymph nodes of sarcoidosis patients compared with controls. An animal model has shown that *P. acnes* can induce a granulomatous response in mice similar to sarcoidosis. Others have demonstrated the presence of a mycobacterial protein (*Mycobacterium tuberculosis* catalase peroxidase) in the granulomas of some sarcoidosis patients. This protein is very resistant to degradation and may represent the persistent antigen in sarcoidosis. Immune response to this and other mycobacterial proteins has been documented by another laboratory. These studies suggest that a *Mycobacterium* similar to *M. tuberculosis* could be responsible for sarcoidosis. The mechanism of exposure/infection with such agents has been the focus of other studies. Environmental exposures to insecticides and mold have been associated with an increased risk for disease. In addition, health care workers appear to have an increased risk. Also, sarcoidosis in a donor organ has occurred after transplantation into a sarcoidosis patient. Some authors have suggested that sarcoidosis is not due to a single agent but represents a particular host response to multiple agents. Some studies have been able to correlate the environmental exposures to genetic markers. These studies have supported the hypothesis that a genetically susceptible host is a key factor in the disease. Although helper T cells may be increased, particularly in the lung of patients with sarcoidosis, it is not a monoclonal or malignant expansion of cells.

VIII-70. **The answer is D.** *(Chap. 360)* Lung involvement occurs in >90% of sarcoidosis patients and is by far the most common manifestation of sarcoidosis. Characteristic CT features include peribronchial thickening and reticulonodular changes, which are predominantly subpleural. The peribronchial thickening seen on CT scan seems to explain the high yield of granulomas from bronchial biopsies performed for diagnosis. Usually the infiltrates in sarcoidosis are predominantly an upper lobe process. Approximately one-half of sarcoidosis patients present with obstructive disease, reflected by a reduced ratio of forced expiratory volume in 1 second to forced vital capacity. Cough is a common symptom. Airway involvement causing varying degrees of obstruction underlies the cough in most sarcoidosis patients. Pulmonary arterial hypertension is reported in at least 5% of sarcoidosis patients. Either direct vascular involvement or the consequence of fibrotic changes in the lung can lead to pulmonary arterial hypertension. In sarcoidosis patients with end-stage fibrosis awaiting lung transplant, 70% will have pulmonary arterial hypertension. This is a much higher incidence than that reported for other fibrotic lung diseases. In less advanced, but still symptomatic, patients, pulmonary arterial hypertension has been noted in up to 50% of the cases. Because sarcoidosis-associated pulmonary arterial hypertension may respond to therapy, evaluation for this should be considered in persistently dyspneic patients.

VIII-71. **The answer is D.** *(Chap. 390)* Hypercalcemia and/or hypercalciuria occurs in about 10% of sarcoidosis patients. It is more common in whites than African Americans and in men. The mechanism of abnormal calcium metabolism is increased production of 1,25-dihydroxyvitamin D by the granuloma itself. The 1,25-dihydroxyvitamin D causes increased intestinal absorption of calcium, leading to hypercalcemia with a suppressed parathyroid hormone level. Increased exogenous vitamin D from diet or sunlight exposure may exacerbate this problem. Serum calcium should be determined as part of the initial evaluation of all sarcoidosis patients, and a repeat determination may be useful during the summer months with increased sun exposure.

VIII-72. **The answer is B.** *(Chap. 361)* IgG4-related disease (IgG4-RD) usually presents subacutely, and even in the setting of multiorgan disease most patients do not have fevers or dramatic elevations of C-reactive protein levels (Table VIII-72). Some patients, however, experience substantial weight loss over periods of months. Clinically apparent disease can evolve over months, years, or even decades before the manifestations within a given organ become sufficiently severe to bring the patient to medical attention. Type 1 autoimmune pancreatitis is characteristic of IgG4-RD. Patients with type 1 autoimmune pancreatitis may have their major disease focus in the pancreas; however, thorough evaluations by history, physical examination, blood tests, and cross-sectional imaging may demonstrate lacrimal gland enlargement, sialadenitis, lymphadenopathy, a variety of pulmonary findings, tubulointerstitial nephritis, hepatobiliary disease, aortitis, retroperitoneal fibrosis, or other organ involvement. Two common characteristics of IgG4-RD

TABLE VIII-72 **Organ Manifestations of IgG4-Related Disease**

Organ	Major Clinical Features
Orbits and periorbital tissues	Painless eyelid or periocular tissue swelling; orbital pseudotumor; dacryoadenitis; dacryocystitis; orbital myositis; and mass lesions extending into the pterygopalatine fossa and infiltrating along the trigeminal nerve
Ears, nose, and sinuses	Allergic phenomena (nasal polyps, asthma, allergic rhinitis, peripheral eosinophilia); nasal obstruction, rhinorrhea, anosmia, chronic sinusitis; occasional bone-destructive lesions
Salivary glands	Submandibular and/or parotid gland enlargement (isolated bilateral submandibular gland involvement more common); minor salivary glands sometimes involved
Meninges	Headache, radiculopathy, cranial nerve palsies, or other symptoms resulting from spinal cord compression; tendency to form mass lesions; MRI shows marked thickening and enhancement of dura
Hypothalamus and pituitary	Clinical syndromes resulting from involvement of the hypothalamus and pituitary, e.g., anterior pituitary hormone deficiency, central diabetes insipidus, or both; imaging reveals thickened pituitary stalk or mass formation on the stalk, swelling of the pituitary gland, or mass formation within the pituitary
Lymph nodes	Generalized lymphadenopathy or localized disease adjacent to a specific affected organ; the lymph nodes involved are generally 1–2 cm in diameter and nontender
Thyroid gland	Riedel thyroiditis; fibrosing variant of Hashimoto thyroiditis
Lungs	Asymptomatic finding on lung imaging; cough, hemoptysis, dyspnea, pleural effusion, or chest discomfort; associated with parenchymal lung involvement, pleural disease, or both; four main clinical lung syndromes: inflammatory pseudotumor, paravertebral mass often extending over several vertebrae, central airway disease, localized or diffuse interstitial pneumonia; pleural lesions have severe, nodular thickening of the visceral or parietal pleura with diffuse sclerosing inflammation, sometimes associated with pleural effusion
Aorta	Asymptomatic finding on radiologic studies; surprise finding at elective aortic surgery; aortic dissection; clinicopathologic syndromes described include lymphoplasmacytic aortitis of thoracic or abdominal aorta, aortic dissection, periaortitis and periarteritis, and inflammatory abdominal aneurysm
Retroperitoneum	Backache, lower abdominal pain, lower extremity edema, hydronephrosis from ureteral involvement, asymptomatic finding on radiologic studies; classic radiologic appearance is periaortic inflammation extending caudally to involve the iliac vessels
Kidneys	Tubulointerstitial nephritis; membranous glomerulonephritis in a small minority; asymptomatic tumoral lesions, typically multiple and bilateral, are sometimes detected on radiologic studies; renal involvement strongly associated with hypocomplementemia
Pancreas	Type 1 autoimmune pancreatitis, presenting as mild abdominal pain; weight loss; acute, obstructive jaundice, mimicking adenocarcinoma of the pancreas (including a pancreatic mass); between 20 and 50% of patients present with acute glucose intolerance; imaging shows diffuse (termed "sausage-shaped pancreas") or segmental pancreatic enlargement, with loss of normal lobularity; a mass often raises the suspicion of malignancy
Biliary tree and liver	Obstructive jaundice associated with autoimmunity in most cases; weight loss; steatorrhea; abdominal pain; and new-onset diabetes mellitus; mimicker of primary sclerosing cholangitis and cholangiocarcinoma
Other organs involved	Gallbladder, liver (mass), breast (pseudotumor), prostate (prostatism), pericardium (constrictive pericarditis), mesentery (sclerosing mesenteritis), mediastinum (fibrosing mediastinitis), skin (erythematous or flesh-colored papules), peripheral nerve (perineural inflammation)

are allergic disease and the tendency to form tumefactive lesions that mimic malignancies, such as orbital pseudotumor. In the kidneys, tubulointerstitial nephritis is reported and rarely membranous glomerulonephritis, but not crescentic glomerulonephritis.

VIII-73. **The answer is D.** *(Chap. 361)* This patient has IgG4-related disease (IgG4-RD). IgG4-RD is a fibroinflammatory condition characterized by a tendency to form tumefactive lesions. The clinical manifestations of this disease, however, are protean and continue to be defined. Pancreatic and retroperitoneal involvement is well described and may present as type 1 autoimmune pancreatitis, presenting as mild abdominal pain, weight loss, and acute, obstructive jaundice, mimicking adenocarcinoma of the pancreas (including a pancreatic mass). Imaging shows diffuse (termed sausage-shaped pancreas) or segmental pancreatic enlargement, with loss of normal lobularity; a mass often raises the suspicion of malignancy. The key histopathology characteristics of IgG4-RD are a dense lymphoplasmacytic infiltrate that is organized in a storiform pattern (resembling a basket weave), obliterative phlebitis, and a mild to moderate eosinophilic infiltrate. The inflammatory infiltrate is composed of an admixture of B and T lymphocytes. B cells are typically organized in germinal centers. Plasma cells staining for CD19, CD138, and IgG4 appear to radiate out from the germinal centers. Vital organ involvement must be treated aggressively, however, because IgG4-RD can lead to serious organ dysfunction and failure. Aggressive disease can lead quickly to end-stage liver disease, permanent impairment of pancreatic function, renal atrophy, aortic dissection or aneurysms, and destructive lesions in the sinuses and nasopharynx. Glucocorticoids are the first line of therapy. Treatment regimens, extrapolated from experience with the management of autoimmune pancreatitis, generally begin with 40 mg/d of prednisone, with tapering to discontinuation or maintenance doses of 5 mg/d within 2 or 3 months. The clinical response to glucocorticoids is usually swift and striking; however, longitudinal data indicate that disease flares occur in more than 90% of patients within 3 years. Conventional steroid-sparing agents such as azathioprine and mycophenolate mofetil have been used in some patients; however, evidence for their efficacy is lacking.

VIII-74. **The answer is B.** *(Chap. 362)* Muckle-Wells syndrome (MWS), hyperimmunoglobulinemia D with periodic fever syndrome (HIDS), and tumor necrosis factor (TNF)-receptor-associated periodic syndrome (TRAPS) are inherited disorders that lead to excess activation of inflammasomes and increased downstream interleukin (IL)-1 signaling. Thus, canakinumab, an IL-1 inhibitor, is useful in these syndromes. Etanercept, a TNF-inhibitor, ameliorates TRAPS attacks, but the long-term experience with this agent has been less favorable. IL-1 inhibition has been beneficial in a large percentage of the patients in whom it has been used, and canakinumab recently received U.S. Food and Drug Administration approval for the treatment of TRAPS. Monoclonal anti-TNF antibodies like adalimumab should be avoided, because they may exacerbate TRAPS attacks. Rituximab, which targets CD20 on B cells, is not useful in these disorders of innate immunity. Colchicine works well in another periodic fever syndrome, Familial Mediterranean Fever, but is not the preferred agent for MWS, HIDS, or TRAPS. Lisinopril is an angiotensin-converting enzyme-inhibitor and not useful for treating the inflammation of these disorders.

VIII-75. **The answer is A.** *(Chap. 362)* Familial Mediterranean fever (FMF) is the prototype of a group of inherited diseases that are characterized by recurrent episodes of fever with serosal, synovial, or cutaneous inflammation. The *FMF* gene encodes a 781-amino acid, ~95-kDa protein denoted pyrin (or marenostrin) that is expressed in granulocytes, eosinophils, monocytes, dendritic cells, and synovial and peritoneal fibroblasts. Typical FMF episodes generally last 24–72 hours, with arthritic attacks tending to last somewhat longer. In some patients, the episodes occur with great regularity, but more often, the frequency of attacks varies over time, ranging from as often as once every few days to remissions lasting several years. Attacks are often unpredictable, although some patients relate them to physical exertion, emotional stress, or menses; pregnancy may be associated with remission. If measured, fever is nearly always present throughout FMF attacks. Severe hyperpyrexia and even febrile seizures may be seen in infants, and fever is sometimes the only manifestation of FMF in young children. Over 90% of FMF patients experience abdominal attacks at some time. Episodes range in severity from dull, aching pain and distention with mild tenderness on direct palpation to severe, generalized pain with absent bowel sounds, rigidity, rebound tenderness, and air-fluid levels on upright radiographs. CT scanning may demonstrate a small amount of fluid in the abdominal cavity. If such patients undergo exploratory laparotomy, a sterile, neutrophil-rich peritoneal exudate is present, sometimes with adhesions from previous episodes. Ascites is rare. Exercise-induced (nonfebrile) myalgia is common in FMF, and a small percentage of patients develop a protracted febrile myalgia that can last several weeks.

VIII-76. **The answer is A.** *(Chap. 362)* The treatment of choice for FMF is daily oral colchicine, which decreases the frequency and intensity of attacks and prevents the development of amyloidosis in compliant patients. Intermittent dosing at the onset of attacks is not as effective as daily prophylaxis and is of unproven value in preventing amyloidosis. The usual adult dose of colchicine is 1.2–1.8 mg/d, which causes substantial reduction in symptoms in two-thirds of patients and some improvement in >90%. Children may require lower doses, although not proportionately to body weight.

VIII-77. **The answer is C.** *(Chap. 364)* Osteoarthritis (OA) is the most common type of arthritis. Its high prevalence, especially in the elderly, and its negative impact on physical function make it a leading cause of disability in the elderly. Because of the aging of Western populations and because obesity, a major risk factor, is increasing in prevalence, the occurrence of OA is on the rise. Symptomatic OA of the knee (pain on most days of a recent month plus x-ray evidence of OA in that knee) occurs in ~12% of persons age ≥60 in the United States and 6% of all adults age ≥30. Symptomatic hip OA is roughly one-third as common as disease in the knee. Although radiographic hand OA and the appearance of bony enlargement in affected hand joints are extremely common in older persons, most cases are often not symptomatic. Even so, symptomatic hand OA occurs in ~10% of elderly individuals and often produces measurable limitation in function.

VIII-78. **The answer is E.** *(Chap. 364)* Osteoarthritis (OA) affects certain joints, yet spares others. Commonly, affected joints include the cervical and lumbosacral spine, hip, knee, and first metatarsal phalangeal joint (Figure VIII-78). In the hands, the distal and proximal interphalangeal joints and the base of the thumb are often affected. Usually spared are the wrist, elbow, and ankle. Human joints were designed, in an evolutionary sense, for brachiating apes, animals that still walked on four limbs. We thus develop OA in joints that were ill designed for human tasks such as pincer grip (OA in the thumb base) and walking upright (OA in knees and hips). Some joints, like the ankles, may be spared because their articular cartilage may be uniquely resistant to loading stresses.

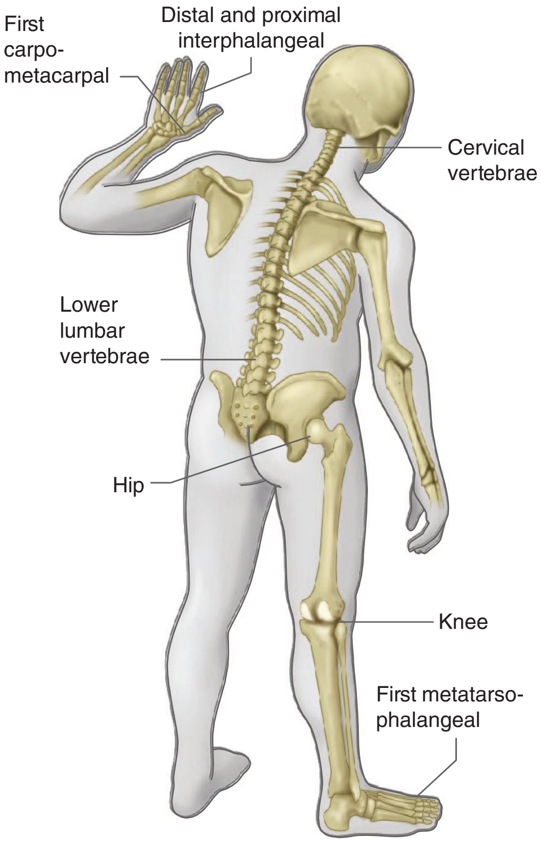


FIGURE VIII-78

VIII-79. **The answer is D.** *(Chap. 364)* Examination of the synovial fluid is often helpful in suspected osteoarthritis (OA), particularly if inflammatory disease is possible. If the synovial fluid white blood cell count is >1000/μL, inflammatory arthritis, gout, or pseudogout is likely, with the latter two being also identified by the presence of crystals. Because cartilage is aneural, cartilage loss in a joint is not accompanied by pain. Thus, pain in OA likely arises from structures outside the cartilage. Innervated structures in the joint include the synovium, ligaments, joint capsule, muscles, and subchondral bone. Most of these are not visualized by the x-ray, and the severity of radiographic changes in OA correlates poorly with pain severity. OA is the most common type of arthritis. Its high prevalence, especially in the elderly, and the high rate of disability related to disease make it a leading cause of disability in the elderly. Although MRI may reveal the extent of pathology in an osteoarthritic joint, it is not indicated as part of the diagnostic workup.

VIII-80. **The answer is C.** *(Chap. 364)* Recent guidelines recommend against the use of glucosamine or chondroitin for osteoarthritis (OA). Large publicly supported trials have failed to show that, compared with placebo, these compounds relieve pain in persons with disease. Glucocorticoid injections are efficacious in OA, but response is variable, with some patients having little relief of pain, whereas others experience pain relief lasting several months. Glucocorticoid injections are useful to get patients over acute flares of pain and may be especially indicated if the patient has coexistent OA and crystal deposition disease, especially from calcium pyrophosphate dihydrate crystals. Acetaminophen (paracetamol) is the initial analgesic of choice for patients with OA in knees, hips, or hands. For some patients, it is adequate to control symptoms, in which case more toxic drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs) can be avoided. Doses up to 1 g three times daily can be used. NSAIDs are the most popular drugs to treat OA pain. They can be administered either topically or orally. In clinical trials, oral NSAIDs produced approximately 30% greater improvement in pain than high-dose acetaminophen. Ultimately, when the patient with knee or hip OA has failed medical treatment modalities and remains in pain, with limitations of physical function that compromise the quality of life, the patient should be referred for total knee or hip arthroplasty. These are highly efficacious operations that relieve pain and improve function in the vast majority of patients, although rates of success are higher for hip than knee replacement.

VIII-81. **The answer is A.** *(Chap. 365)* Calcium pyrophosphate deposition disease (CPPD) arthropathy may be asymptomatic, acute, subacute, or chronic or may cause acute synovitis superimposed on chronically involved joints. Acute CPPD arthritis originally was termed *pseudogout* by McCarty and co-workers because of its striking similarity to gout. The knee is the joint most frequently affected in CPPD arthropathy. Other sites include the wrist, shoulder, ankle, elbow, and hands. The temporomandibular joint may be involved. Clinical and radiographic evidence indicates that CPPD deposition is polyarticular in at least two-thirds of patients. If radiographs or ultrasound reveal punctate and/or linear radiodense deposits within fibrocartilaginous joint meniscus or articular hyaline cartilage (*chondrocalcinosis*), the diagnostic likelihood of CPPD disease is further increased. *Definitive diagnosis* requires demonstration of typical rhomboid or rodlike crystals (generally weakly positively birefringent or nonbirefringent with polarized light) in synovial fluid or articular tissue. In the absence of joint effusion or indications to obtain a synovial biopsy, chondrocalcinosis is presumptive of CPPD. In patients with an inflammatory monoarthritis crystalline arthritis like CPPD, gout must be considered, as well as septic arthritis. This patient had no other features suggestive of septic arthritis. Her age, sex, and the chondrocalcinosis make pseudogout more likely than gout. Rheumatoid arthritis is most often a polyarthritis and commonly presents in the third through fifth decades of life.

VIII-82. **The answer is E.** *(Chap. 365)* The micrograph illustrates extracellular and intracellular monosodium urate crystals with needle- and rod-shaped crystals (Figure VIII-82B). These crystals are strongly negative birefringent crystals under compensated polarized light microscopy. This is gout. Most patients with gout are overproducers of uric acid. Hyaline cartilage degeneration is typical of osteoarthritis, which usually has a bland synovial aspirate. Antibodies to antinuclear antibodies are typical of lupus, rare in an elderly man, and not associated with crystalline fluid. Bacterial joint infection would have a purulent synovial fluid with prominent neutrophils. Increased production of inorganic pyrophosphate is a cause of calcium pyrophosphate deposition disease (CPPD; pseudogout), another crystalline arthropathy. CPPD crystals are shown below.

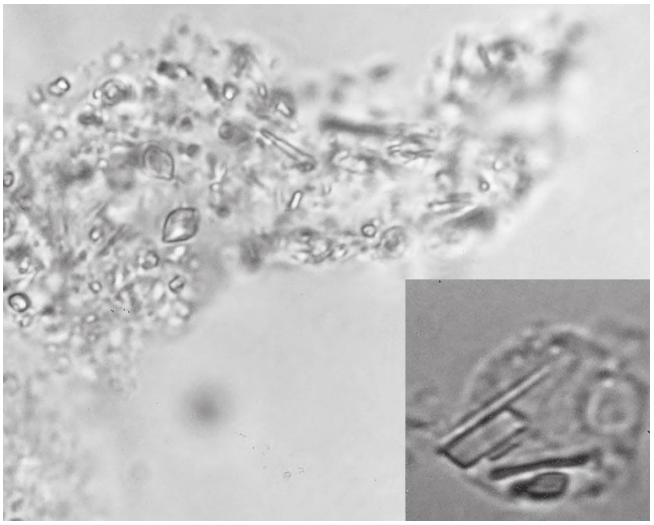


FIGURE VIII-82B Intracellular and extracellular calcium pyrophosphate (CPP) crystals, as seen in a fresh preparation of synovial fluid, illustrate rectangular, rod-shaped, and rhomboid crystals that are weakly positively or nonbirefringent crystals (compensated polarized light microscopy; ×400 magnification).

VIII-83. The answer is C. *(Chap. 365)* The xanthine oxidase inhibitor allopurinol is by far the most commonly used hypouricemic agent and is the best drug to lower serum urate in overproducers, urate stone formers, and patients with renal disease. It can be given in a single morning dose, usually 100 mg initially and increasing up to 800 mg if needed. In patients with chronic renal disease, the initial allopurinol dose should be lower and adjusted depending on the serum creatinine concentration; for example, with a creatinine clearance of 10 mL/min, one generally would use 100 mg every other day. Doses can be increased gradually to reach the target urate level of <6 mg/dL. Toxicity of allopurinol has been recognized increasingly in patients who use thiazide diuretics, in patients allergic to penicillin and ampicillin, and in Asians expressing HLA-B*5801. Colchicine is commonly used with allopurinol in the treatment of gout. Allopurinol and azathioprine should not be coprescribed because azathioprine can greatly increase blood levels of allopurinol and lead to toxicity.

VIII-84. The answer is E. *(Chap. 366)* The pain of fibromyalgia (FM) is associated with tenderness and increased evoked pain sensitivity. In clinical practice, this elevated sensitivity may be identified by pain induced by the pressure of a blood pressure cuff or skin roll tenderness. More formally, an examiner may complete a tender-point examination in which the examiner uses the thumbnail to exert pressure of ~4 kg/m^2 (or the amount of pressure leading to blanching of the tip of the thumbnail) on well-defined musculotendinous sites. Routine laboratory and radiographic tests yield normal results in FM; thus, diagnostic testing is focused on exclusion of other diagnoses and evaluation for pain generators or comorbid conditions (Table VIII-84). Most patients with new chronic widespread pain should be assessed for the most common entities in the differential diagnosis. Radiographic testing should be used sparingly and only for diagnosis of inflammatory arthritis. After the patient has been evaluated thoroughly, repeat testing is discouraged unless the symptom complex changes. Particularly to be discouraged is MRI of the spine unless there are features suggesting inflammatory spine disease or neurologic symptoms.

VIII-85. The answer is C. *(Chap. 366)* This patient presents with a characteristic history for fibromyalgia, a diffuse pain syndrome associated with increased sensitivity to evoked pain. The underlying pathophysiology of pain in fibromyalgia is felt to be related to altered pain processing in the central nervous system. Epidemiologically, women are affected nine times more frequently than men. The worldwide prevalence of fibromyalgia is 2–3%,

TABLE VIII-84 Laboratory and Radiographic Testing in Patients with Fibromyalgia Symptoms

Routine
Erythrocyte sedimentation rate or C-reactive protein
Complete blood count
Thyroid-stimulating hormone
Guided by History and Physical Examination
Complete metabolic panel
Antinuclear antibody
Anti-SSA and anti-SSB
Rheumatoid factor and anti–cyclic citrullinated peptide
Creatine phosphokinase
Viral (e.g., Hepatitis C, HIV) and bacterial (e.g., Lyme) serologies
Spine and joint radiographs

Abbreviations: Anti-SSA, anti–Sjögren syndrome A; anti-SSB, anti–Sjögren syndrome B.
Source: Data from Arnold LM et al: *J Women's Health* 21:231, 2012; Fitzcharles MA et al: *J Rheumatol* 40:1388, 2013.

but in primary care practices, it is as high as 5–10%. The disorder is even more common in patients with degenerative or inflammatory rheumatic disorders, with a prevalence of 20% or higher. The most common presenting complaint is diffuse pain that is difficult to localize. Pain is both above and below the waist and affects the extremities as well as the axial skeleton. However, it does not localize to a specific joint. The pain is noted to be severe in intensity and difficult to ignore and interferes with daily functioning. Although this patient demonstrates pain at several tender points, the American College of Rheumatology no longer includes tender point assessment in the diagnostic criteria for fibromyalgia. Rather, the new criteria focus on clinical symptoms of widespread pain and neuropsychological symptoms that have been present for at least 3 months. Some of the neuropsychological conditions that are frequently observed in fibromyalgia include sleep disturbance, impaired cognitive functioning, fatigue, stiffness, anxiety, and depression. The lifetime prevalence of mood disorders in patients with fibromyalgia is 80%. Sleep disturbances can include difficulty falling asleep, difficulty staying asleep, or nonrestorative sleep, among others.

VIII-86. The answer is D. *(Chap. 366)* Fibromyalgia is a common disorder affecting 2–5% of the population. It presents as a diffuse pain syndrome with associated neuropsychological symptoms including depression, anxiety, fatigue, cognitive dysfunction, and disturbed sleep. Treatment for fibromyalgia should include a combination of nonpharmacologic and pharmacologic approaches. Patient education regarding the disease is important to provide a framework for understanding symptoms. The focus of treatment should not be on eliminating pain but improving function and quality of life. Physical conditioning is an important part of improving function and should include a multifaceted exercise program with aerobic exercise, strength training, and exercises that incorporate relaxation techniques such as yoga or tai chi. Cognitive behavioral therapy can be useful in improving sleep disturbance and also for decreasing illness behaviors. Pharmacologic therapy in fibromyalgia is targeted at the afferent and efferent pain pathways. The two most common categories of medications for fibromyalgia are antidepressants and anticonvulsants. Amitriptyline, duloxetine, and milnacipran have all been used with some efficacy in fibromyalgia. Duloxetine and milnacipran are approved by the U.S. Food and Drug Administration (FDA) for the treatment of fibromyalgia. The anticonvulsants that are predominantly used in fibromyalgia are those that are ligands of the α-2-δ subunit of voltage-gated calcium channels. These include gabapentin and pregabalin, which are also FDA approved for treatment of fibromyalgia. Anti-inflammatory medications and glucocorticoids are not effective in fibromyalgia. However, if there is a comorbid triggering condition such as rheumatoid arthritis, appropriate therapy directed at the underlying disorder is critical to controlling symptoms of fibromyalgia as well. Opioid analgesics such as oxycodone should be avoided. They have no efficacy in treating fibromyalgia and may induce hyperalgesia that can worsen both pain and function.

VIII-87. The answer is C. *(Chap. 367)* Neuropathic joint disease (Charcot joint) is a progressive destructive arthritis associated with loss of pain sensation, proprioception, or both. Normal muscular reflexes that modulate joint movement are impaired. Without these protective mechanisms, joints are subjected to repeated trauma, resulting in progressive cartilage and bone damage. Today, diabetes mellitus is the most frequent cause of neuropathic joint disease (Table VIII-87). A variety of other disorders are associated with neuropathic arthritis, including tabes dorsalis, leprosy, yaws, syringomyelia, meningomyelocele, congenital indifference to pain, peroneal muscular atrophy (Charcot-Marie-Tooth disease), and amyloidosis. An arthritis resembling neuropathic joint disease has been reported in patients who have received intra-articular glucocorticoid injections, but this is a rare complication and was not observed in one series of patients with knee osteoarthritis who received intra-articular glucocorticoid injections every 3 months for 2 years. The distribution of joint involvement depends on the underlying neurologic disorder. In tabes dorsalis, the knees, hips, and ankles are most commonly affected; in syringomyelia, the glenohumeral joint, elbow, and wrist; and in diabetes mellitus, the tarsal and tarsometatarsal joints.

TABLE VIII-87 Disorders Associated With Neuropathic Joint Disease

Diabetes mellitus	Amyloidosis
Tabes dorsalis	Leprosy
Meningomyelocele	Congenital indifference to pain
Syringomyelia	Peroneal muscular atrophy

VIII-88. The answer is A. *(Chap. 367)* The finding shown in Figure VIII-88 is characteristic of clubbing. Clubbing occurs in the distal portions of the digits and is characterized by widening of the fingertips, convexity of the nail contour, and loss of the normal 15-degree angle between the proximal nail and cuticle. Clinically, it can be sometimes difficult to ascertain whether clubbing is present. One approach to the diagnosis of clubbing is to measure the diameter of the finger at the base of the nail and at the tip of the finger in all 10 fingers. For each finger, a ratio between the base of the nail and the tip of the finger is determined. If the sum of all 10 fingers is greater than 1, then clubbing is felt to be present. A simpler approach is to have an individual place the dorsal surfaces of the distal fourth digits from each hand together. In a normal individual, there should be a diamond-shaped space between the digits. When an individual has clubbing, this space is obliterated. Clubbing most commonly occurs in advanced lung disease, especially bronchiectasis, cystic fibrosis, and interstitial lung diseases like sarcoidosis or idiopathic pulmonary fibrosis. Clubbing was originally described in individuals with empyema and can occur in chronic lung infections, including lung abscess, tuberculosis, or fungal infections. Pulmonary vascular lesions and lung cancer also are associated with clubbing. However, chronic obstructive pulmonary disease does not cause clubbing. However, the causes of clubbing are not limited to the pulmonary system alone. Clubbing can be a benign familial condition and is also associated with a variety of other disorders, including cyanotic congenital heart disease; subacute bacterial endocarditis; Crohn disease; ulcerative colitis; celiac disease; and cancer of the esophagus, liver, small bowel, and large bowel. In untreated hyperthyroidism, clubbing can occur in association with periostitis in a condition called thyroid acropachy. Although these numerous clinical associations have been described for many centuries, the cause of clubbing remains unknown.

VIII-89. The answer is C. *(Chap. 367)* Symptoms of hemochromatosis usually begin between the ages of 40 and 60 but can appear earlier. Arthropathy, which occurs in 20–40% of patients, usually begins after the age of 50 and may be the first clinical feature of hemochromatosis. The arthropathy is an osteoarthritis-like disorder affecting the small joints of the hands and later the larger joints, such as knees, ankles, shoulders, and hips. The second and third metacarpophalangeal joints of both hands are often the first and most prominent joints affected; this clinical picture may provide an important clue to the possibility of hemochromatosis because these joints are not predominantly affected by "routine" osteoarthritis. Patients experience some morning stiffness and pain with use of involved joints. The affected joints are enlarged and mildly tender. Radiographs show narrowing of the joint space, subchondral sclerosis, subchondral cysts, and juxta-articular proliferation of bone. Hooklike osteophytes are seen in up to 20% of patients; although they are regarded as a characteristic feature of hemochromatosis, they can also occur in osteoarthritis and are not disease specific. Bony erosions are typical of rheumatoid arthritis, not hemochromatosis. The synovial fluid is noninflammatory. In approximately half of patients, there is evidence of calcium pyrophosphate deposition disease, and some patients experience episodes of acute pseudogout late in the course of disease *(Chap. 365)*. The treatment of hemochromatosis is repeated phlebotomy. Unfortunately, this treatment has little effect on established arthritis, which, along with chondrocalcinosis, may progress. Symptom-based treatment of the arthritis consists of administration of acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), as tolerated. Acute pseudogout attacks are treated with high doses of an NSAID or a short course of glucocorticoids. Hip or knee total joint replacement has been successful in advanced disease.

VIII-90. **The answer is B.** *(Chap. 368)* Bursitis is inflammation of a bursa, which is a thin-walled sac lined with synovial tissue. The function of the bursa is to facilitate movement of tendons and muscles over bony prominences. Excessive frictional forces from overuse, trauma, systemic disease (e.g., rheumatoid arthritis, gout), or infection may cause bursitis. *Subacromial bursitis* (subdeltoid bursitis) is the most common form of bursitis. Other forms of bursitis include trochanteric bursitis, olecranon bursitis, Achilles bursitis, and retrocalcaneal bursitis. Bursitis is typically diagnosed by history and physical examination, but visualization by ultrasound may play a useful role in selected instances for diagnosis and directed guidance of glucocorticoid injection. Treatment of bursitis consists of prevention of any aggravating situation, rest of the involved part, administration of a nonsteroidal anti-inflammatory drug where appropriate for an individual patient, or local glucocorticoid injection. Fibromyalgia is a chronic pain syndrome. It does not cause inflammation of the joints or related structures, like the bursa, so it would not be a cause for bursitis.

VIII-91. **The answer is E.** *(Chap. 368)* Lateral epicondylitis, also known as tennis elbow, is a painful condition involving the soft tissue over the lateral aspect of the elbow. The pain originates at or near the site of attachment of the common extensors to the lateral epicondyle and may radiate into the forearm and dorsum of the wrist. The pain usually appears after work or recreational activities involving repeated motions of wrist extension and supination against resistance. Most patients with this disorder injure themselves in activities other than tennis, such as pulling weeds, carrying suitcases or briefcases, or using a screwdriver. The injury in tennis usually occurs when hitting a backhand with the elbow flexed. Shaking hands and opening doors can reproduce the pain. Striking the lateral elbow against a solid object may also induce pain. The treatment is usually rest along with administration of an nonsteroidal anti-inflammatory drugs. Ultrasound, icing, and friction massage may also help relieve pain. When pain is severe, the elbow is placed in a sling or splint at 90° of flexion. When the pain is acute and well localized, injection of a glucocorticoid using a small-gauge needle may be effective. Following injection, the patient should be advised to rest the arm for at least 1 month and avoid activities that would aggravate the elbow. Once symptoms have subsided, the patient should begin rehabilitation to strengthen and increase flexibility of the extensor muscles before resuming physical activity involving the arm. A forearm band placed 2.5–5.0 cm (1–2 inches) below the elbow may help to reduce tension on the extensor muscles at their attachment to the lateral epicondyle. The patient should be advised to restrict activities requiring forcible extension and supination of the wrist. Improvement may take several months. The patient may continue to experience mild pain but, with care, can usually avoid the return of debilitating pain. Occasionally, surgical release of the extensor aponeurosis may be necessary. Methotrexate and adalimumab are used to treat a variety of autoimmune diseases including rheumatoid arthritis. These drugs are not appropriate treatment for lateral epicondylitis.

VIII-92. **The answer is B.** *(Chap. 368)* This patient presents with inflammation of the iliotibial band. The iliotibial band is a thick connective tissue that runs along the outer thigh from the ilium to the fibula. When this band becomes tightened or inflamed, pain most commonly occurs where the band passes over the lateral femoral condyle of the knee, leading to a burning or aching pain in this area that can radiate toward the outer thigh. This overuse injury is most often seen in runners and can be caused by improperly fitted shoes, running on uneven surfaces, and excessive running. It is also more common in individuals with a varus alignment of the knee (bowlegged). Treatment of iliotibial band syndrome involves rest, nonsteroidal anti-inflammatory drugs, physical therapy, and addressing risk factors such as poorly fitted shoes or uneven running surface. Glucocorticoid injection at the lateral femoral condyle may alleviate pain, but running must strictly be avoided for 2 weeks following injection. In refractory cases, surgical release of the iliotibial band may be beneficial.

VIII-93. The answer is A. *(Chap. 368)* Adhesive capsulitis, or "frozen shoulder," is characterized by pain and restricted motion of the shoulder. Usually this occurs in the absence of intrinsic shoulder disease, including osteoarthritis and avascular necrosis. It is, however, more common in patients who have had bursitis or tendinitis previously as well as patients with other systemic illnesses, such as chronic pulmonary disease, ischemic heart disease, and diabetes mellitus. The etiology is not clear, but adhesive capsulitis appears to develop in the setting of prolonged immobility. Reflex sympathetic dystrophy may also occur in the setting of adhesive capsulitis. Clinically, this disorder is more commonly seen in females over age 50. Pain and stiffness develop over the course of months to years. On physical examination, the affected joint is tender to palpation, with a restricted range of motion. The gold standard for diagnosis is arthrography with limitation of the amount of injectable contrast to less than 15 mL. In most patients, adhesive capsulitis will regress spontaneously within 1 to 3 years. Nonsteroidal anti-inflammatory drugs, glucocorticoid injections, physical therapy, and early mobilization of the arm are useful therapies.

VIII-94. The answer is B. *(Chap. 368)* Inflammation of the abductor pollicis longus and the extensor pollicis brevis at the radial styloid process tendon sheath is known as De Quervain tenosynovitis. Repetitive twisting of the wrist can lead to this condition. Pain occurs when grasping with the thumb and can extend radially along the wrist to the radial styloid process. Mothers often develop this tenosynovitis by holding their babies with the thumb outstretched. The Finkelstein sign is positive in De Quervain tenosynovitis. It is positive if the patient develops pain by placing the thumb in the palm, closing the fingers around the thumb, and deviating the wrist in the ulnar direction. Management of De Quervain tenosynovitis includes nonsteroidal anti-inflammatory drugs and splinting. Glucocorticoid injections can be effective. A Phalen maneuver is used to diagnose carpal tunnel syndrome and does not elicit pain. The wrists are flexed for 60 seconds to compress the median nerve to elicit numbness, burning, or tingling. Gouty arthritis will present with an acutely inflamed joint with crystal-laden fluid. Rheumatoid arthritis is a systemic illness with characteristic joint synovitis and radiographic features.

VIII-95. The answer is C. *(Chap. 368)* The patient has plantar fasciitis, a diagnosis that often can be made clinically. It is a common cause of foot pain in adults, with the peak incidence occurring in people between the ages of 40 and 60 years. The pain originates at or near the site of the plantar fascia attachment to the medial tuberosity of the calcaneus. Several factors that increase the risk of developing plantar fasciitis include obesity, pes planus (flat foot or absence of the foot arch when standing), pes cavus (high-arched foot), limited dorsiflexion of the ankle, prolonged standing, walking on hard surfaces, and faulty shoes. In runners, excessive running and a change to a harder running surface may precipitate plantar fasciitis. Smoking and oral contraceptives are not specific risk factors. Patients experience severe pain with the first steps on arising in the morning or following inactivity during the day. The pain usually lessens with weight-bearing activity during the day, only to worsen with continued activity. Pain is made worse on walking barefoot or walking up stairs. On examination, maximal tenderness is elicited on palpation over the inferior heel corresponding to the site of attachment of the plantar fascia. Imaging studies may be indicated when the diagnosis is not clear. Plain radiographs may show heel spurs, which are of little diagnostic significance. Ultrasonography in plantar fasciitis can demonstrate thickening of the fascia and diffuse hypoechogenicity, indicating edema at the attachment of the plantar fascia to the calcaneus. MRI is a sensitive method for detecting plantar fasciitis, but it is usually not required for establishing the diagnosis. The differential diagnosis of inferior heel pain includes calcaneal stress fractures, the spondyloarthritides, rheumatoid arthritis, gout, neoplastic or infiltrative bone processes, and nerve compression/entrapment syndromes. Resolution of plantar fasciitis symptoms occurs within 12 months in more than 80% of patients. Initial treatment consists of ice, heat, massage, and stretching. Orthotics providing medial arch support can be effective. A short course of nonsteroidal anti-inflammatory drugs can be given to patients when the benefits outweigh the risks. Local glucocorticoid injections have also been shown to be efficacious but may carry an increased risk for plantar fascia rupture. Plantar fasciotomy is reserved for those patients who have failed to improve after at least 6–12 months of conservative treatment.

SECTION IX

Endocrinology and Metabolism

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

IX-1. Production of which of the following hormones would be most impaired by lesions that affect the pituitary stalk or hypothalamus?

A. Adrenocorticotrophic hormone
B. Growth hormone
C. Oxytocin
D. Prolactin
E. Thyroid-stimulating hormone

IX-2. During lactation, increased levels of prolactin hormone result in all of the following EXCEPT:

A. Anovulation
B. Decreased levels of estrogen
C. Increased gonadal steroidogenesis
D. Shortened luteal phase of menstrual cycle
E. Suppressed gonadotrophin-releasing hormone levels

IX-3. A 45-year-old man reports to his primary care physician that his wife has noted coarsening of his facial features over several years. In addition, he reports low libido and decreased energy. Physical examination shows frontal bossing and enlarged hands. An MRI confirms that he has a pituitary mass. Which of the following screening tests should be ordered to diagnose the cause of the mass?

A. 24-Hour urinary free cortisol
B. Adrenocorticotropic hormone assay
C. Growth hormone level
D. Serum insulin-like growth factor-1 level
E. Serum prolactin level

IX-4. A 75-year-old man presents with the development of abdominal obesity, proximal myopathy, and skin hyperpigmentation over 1–2 months. His laboratory evaluation shows a hypokalemic metabolic alkalosis. Cushing syndrome is suspected. Which of the following statements regarding this syndrome is true?

A. Basal adrenocorticotropic hormone (ACTH) level is likely to be low.
B. Circulating corticotropin-releasing hormone is likely to be elevated.
C. Pituitary MRI will visualize all ACTH-secreting tumors.
D. Referral for urgent performance of inferior petrosal venous sampling is indicated.
E. Serum potassium level <3.3 mmol/L is suggestive of ectopic ACTH production.

IX-5. All of the following are causes of acquired hypopituitarism EXCEPT:

A. Amyloidosis
B. Ipilimumab therapy
C. Sarcoidosis
D. Subarachnoid hemorrhage
E. Systemic lupus erythematosus

IX-6. A 19-year-old man presents to your clinic to establish care. He has short stature, a history of delayed puberty, color blindness, and anosmia. You diagnose him with Kallmann syndrome. Which of the following is the most appropriate treatment?

A. Angiotensin-converting enzyme inhibitor
B. Cyclic estrogen
C. Human chorionic gonadotropin
D. Insulin
E. Thyroid hormone

IX-7. A 22-year-old woman who is otherwise healthy undergoes an uneventful vaginal delivery of a full-term infant. One-day postpartum, she complains of visual changes and severe headache. Two hours after these complaints, she is found unresponsive and profoundly hypotensive. She is intubated and placed on mechanical ventilation. Her blood pressure is 68/28, regular heart rate is 148 beats/min, her oxygen saturation is 95% on FiO_2 of 0.40. Physical examination is unremarkable. Her laboratory tests are notable for glucose of 49 mg/dL, with normal hematocrit and white blood cell count. Which of the following is most likely to reverse her hypotension?

A. Activated drotrecogin alfa
B. Hydrocortisone
C. Piperacillin/tazobactam
D. Thyroxine
E. Transfusion of packed red blood cells

IX-8. You are caring for a 19-year-old man who had a brain tumor when young and underwent cranial radiation. You note that he has short stature and has not yet gone through puberty. You suspect that he has pituitary insufficiency due to radiation. Which of the following statements is true regarding acquired hypopituitarism due to radiation?

A. At a dose of 50 Gy of radiation, only 5% of patients will manifest hypopituitarism.
B. Growth hormone is the most common hormonal deficiency.
C. Older adults are at highest risk from radiation induced hypopituitarism.
D. The majority of patients who develop hypopituitarism after cranial radiation do so within a year of treatment.
E. There is no correlation between radiation dose and likelihood of developing hypopituitarism.

IX-9. A patient visited a local emergency department 1 week ago with a headache. She received a head MRI, which did not reveal a cause for her symptoms, but the final report states "An empty sella is noted. Advise clinical correlation." The patient was discharged from the emergency department with instructions to follow up with her primary care physician as soon as possible. Her headache has resolved, and the patient has no complaints. However, she comes to your office 1 day later very concerned about this unexpected MRI finding. Which of the following should be the next step in her management?

A. Diagnose her with subclinical panhypopituitarism and initiate low-dose hormone replacement.
B. Reassure her and follow laboratory results closely.
C. Reassure her and repeat the MRI in 6 months.
D. This may represent early endocrine malignancy, so whole-body positron emission tomography/CT is indicated.
E. This MRI finding likely represents the presence of a benign adenoma, so she should be referred to neurosurgery for resection.

IX-10. A 35-year-old woman is evaluated for new headaches with a brain MRI. A pituitary lesion is visualized. Which of the following laboratory findings would be suggestive of a functional pituitary adenoma?

A. Decreased free T_4
B. Decreased luteinizing hormone
C. Decreased morning cortisol
D. Elevated prolactin
E. Elevated thyroid-stimulating hormone

IX-11. On MRI of the pituitary, which of the following findings is abnormal in an adult?

A. A slightly concave upper aspect of the pituitary
B. Brighter T1 intensity of the posterior pituitary
C. Heterogeneous anterior pituitary tissue
D. Pituitary height of 8–12 mm
E. Tissue that is lower intensity than the nearby brain tissue on T1 images and enhances on T2 images

IX-12. A 55-year-old man has a pituitary adenoma on imaging that has extended directly superiorly and is compressing his optic chiasm. Which of the following visual field deficits is most likely present?

A. Bilateral inferior visual field deficits
B. Bilateral superior visual field deficits
C. Bitemporal hemianopia
D. Central scotomas bilaterally
E. Right homonymous hemianopia

IX-13. Which of the following conditions may cause diabetes insipidus by a secondary decrease in arginine vasopressin secretion?

A. Craniopharyngioma
B. Lithium
C. Pituitary surgery
D. Psychogenic polydipsia
E. Sarcoid

IX-14. All of the following conditions occur as a result of iodine deficiency EXCEPT:

A. Cretinism
B. Goiter
C. Graves disease
D. Hypothyroidism

IX-15. All of the following are associated with increased levels of total T_4 in the plasma with a normal free T_4 EXCEPT:

A. Cirrhosis
B. Euthyroid sick syndrome
D. Familial dysalbuminemic hyperthyroxinemia
D. Familial excess thyroid binding globulin
E. Pregnancy

IX-16. A 77-year-old woman is transported to the hospital by emergency services. She has decreased consciousness and hypothermia. On examination, her temperature is 35°C (95°F), blood pressure is 130/70, heart rate is 60 beats/min, and respiratory rate 10 breaths/min with oxygen saturation 93% on 4 L nasal oxygen. In addition, her skin is dry and she has hair loss and puffy hands and feet without pitting. Chest radiograph shows a right lobar pneumonia, and thyroid-stimulating hormone level is elevated at 88 mU/L. In addition to antibiotics, what medication should be administered?

A. Hypotonic fluids
B. IV hydrocortisone
C. IV levothyroxine
D. IV Vasopressin
E. B and C

IX-17. Which of the following laboratory findings confirms a diagnosis of secondary hypothyroidism?

A. High thyroid-stimulating hormone (TSH)
B. High unbound T_4 level
C. Low TSH
D. Low unbound T_4 level
E. Normal TSH

IX-18. A 75-year-old woman is diagnosed with hypothyroidism. She has long-standing coronary artery disease and is wondering about the potential consequences for her cardiovascular system. Which of the following statements is true regarding the interaction of hypothyroidism and the cardiovascular system?

A. A reduced stroke volume is found with hypothyroidism.
B. Blood flow is diverted toward the skin in hypothyroidism.
C. Myocardial contractility is increased with hypothyroidism.
D. Pericardial effusions are a rare manifestation of hypothyroidism.
E. Reduced peripheral resistance is found in hypothyroidism and may be accompanied by hypotension.

IX-19. A 38-year-old mother of three presents to her primary care office with complaints of fatigue. She feels that her energy level has been low for the past 3 months. She was previously healthy and taking no medications. She does report that she has gained about 10 lb and has severe constipation, for which she has been taking a number of laxatives. Her thyroid-stimulating hormone level is elevated at 25 mU/L. Free T_4 is low. She is wondering why she has hypothyroidism. Which of the following tests is most likely to diagnose the etiology?

A. Antithyroid peroxidase antibody
B. Antithyroglobulin antibody
C. Radioiodine uptake scan
D. Serum thyroglobulin level
E. Thyroid ultrasound

IX-20. A 45-year-old previously healthy woman presents to the clinic reporting a sore throat. The pain in her throat is referred to her jaw. She has had a fever of 37.8°C (100°F), malaise, and some palpitations. These symptoms started about 1 week prior to presentation. Her children have recently been mildly ill with fever and upper respiratory symptoms. On physical examination, her thyroid is slightly enlarged and very tender to palpation. Laboratory studies show an elevated erythrocyte sedimentation rate of 50 and a thyroid-stimulating hormone level of 0.2 mU/L. Which of the following is the likely cause of her illness?

A. Graves disease
B. Hashimoto thyroiditis
C. Iodine deficiency
D. Subacute thyroiditis (aka viral thyroiditis)
E. Thyroid malignancy

IX-21. A 29-year-old woman is evaluated for anxiety, palpitations, and diarrhea and found to have Graves disease. Before she begins therapy for her thyroid condition, she has an episode of acute chest pain and presents to the emergency department. Although a CT angiogram is ordered, the radiologist calls to notify the treating physician that this is potentially dangerous. Which of the following best explains the radiologist's concern?

A. Iodinated contrast exposure in patients with Graves disease may exacerbate hyperthyroidism.
B. Pulmonary embolism is exceedingly rare in Graves disease.
C. Radiation exposure in patients with hyperthyroidism is associated with increased risk of subsequent malignancy.
D. Tachycardia with Graves disease limits the image quality of CT angiography and will not allow accurate assessment of pulmonary embolism.
E. The radiologist was mistaken; CT angiography is safe in Graves disease.

IX-22. A 65-year-old woman presents to the clinic for her wellness examination. She has no new symptomatic complaints. She has a history of hypertension well controlled on lisinopril. On examination a thyroid nodule larger than 1 cm is palpated. Laboratory studies show a normal thyroid-stimulating hormone level. What is the next step in evaluation?

A. Diagnostic ultrasound with lymph node assessment
B. Fine-needle aspiration of nodule
C. No additional evaluation needed
D. Radionuclide scanning

IX-23. Which of the following is the most common cause of a unilateral adrenal mass?

A. Adrenocortical carcinoma
B. Cortisol-producing adrenocortical adenoma
C. Endocrine-inactive adrenocortical adenoma
D. Lymphoma
E. Pheochromocytoma

IX-24. A 36-year-old man presents to the clinic reporting ankle swelling. On examination, his blood pressure is elevated at 162/86, and he has bilateral ankle edema. There are no other abnormalities on physical examination. Laboratory studies show a potassium of 2.9 and normal creatinine. Which of the following studies is recommended next?

A. AM cortisol
B. CT of adrenals
C. Plasma renin and aldosterone
D. Thyroid-stimulating hormone
E. Urine metanephrines

IX-25. A patient has neurosurgery for a pituitary tumor that requires resection of the gland. Which of the following functions of the adrenal gland will be preserved in this patient immediately postoperatively?

A. Morning peak of plasma cortisol level
B. Release of cortisol in response to stress
C. Sodium retention in response to hypovolemia
D. None of the above

IX-26. Which of the following is the most common cause of Cushing syndrome?

A. Adrenocorticotropic hormone-producing (ACTH) pituitary adenoma
B. Adrenocortical adenoma
C. Adrenocortical carcinoma
D. Ectopic ACTH secretion
E. McCune-Albright syndrome

IX-27. An elderly man is admitted to the hospital after a car accident. His medical history is unknown, and on presentation, he is obtunded and can provide no history. CT scan reveals a splenic laceration, and he is emergently taken to the operating room for splenectomy, which proceeds without complication. At the completion of the operation, all bleeding has stopped, and he returns to the intensive care unit. However, he remains deeply hypotensive with a blood pressure of 70/50 with an increase only to 82/52 after a bolus of 2 L of normal saline IV. He is afebrile with a normal white blood cell count. Repeat CT scan of the chest, abdomen, and pelvis shows no hemorrhage. Jugular venous pressure is not visible above the clavicle. He is obese with a round face and you note abnormalities (Figure IX-27) on his skin examination. Which of the following is the next most appropriate step?

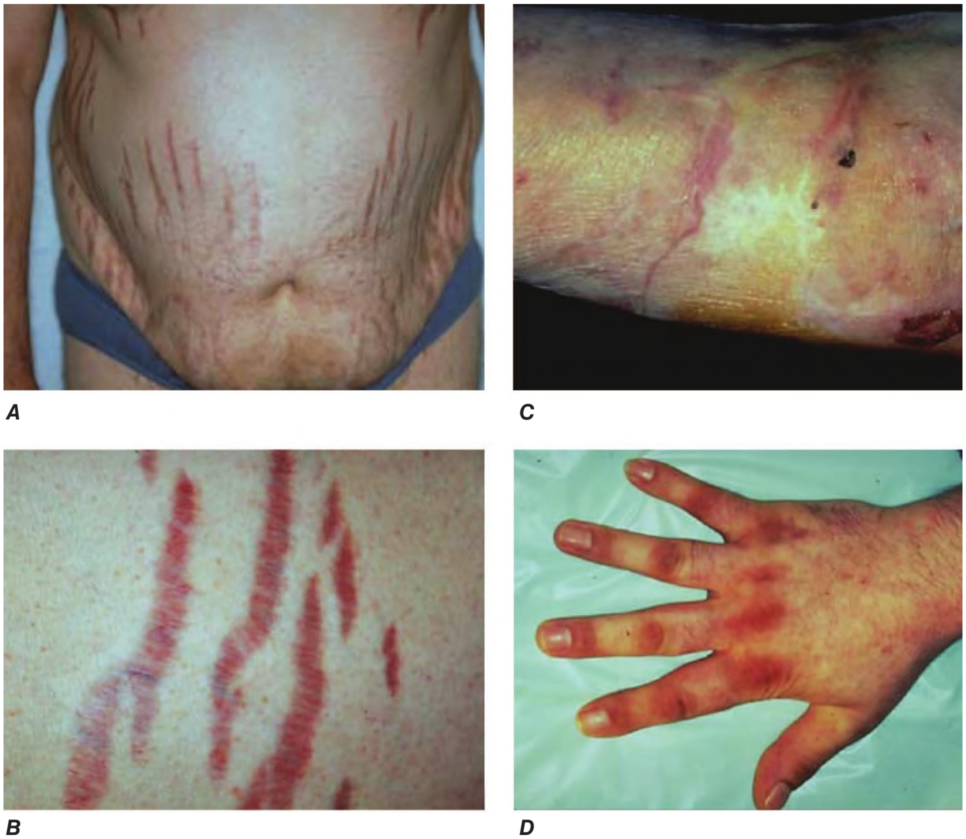


FIGURE IX-27

A. Administer hydrocortisone 100 mg IV
B. Administer vancomycin and piperacillin/tazobactam
C. Insert intra-aortic balloon pump for counterpulsation
D. Perform MRI of the spine
E. Return to the operating room for exploratory laparotomy

IX-28. Which of the following syndromes is associated with development of pheochromocytoma?

A. Multiple endocrine neoplasia type 1
B. Multiple endocrine neoplasia type 2
C. Turner syndrome
D. Von Hippel-Lindau disease
E. B and D

IX-29. A 43-year-old man with episodic, severe hypertension is referred for evaluation of possible secondary causes of hypertension. He reports feeling well generally, except for episodes of anxiety, palpitations, and tachycardia with elevation in his blood pressure during these episodes. Exercise often brings on these events. The patient also has mild depression and his current medications include sertraline, labetalol, amlodipine, and lisinopril. Urine 24-hour total metanephrines are ordered and show an elevation of 1.5 times the upper limit of normal. Which of the following is the next most appropriate step?

A. Hold labetalol for 1 week and repeat testing
B. Hold sertraline for 1 week and repeat testing
C. Refer immediately for surgical evaluation
D. Measure 24-hour urine vanillylmandelic acid level
E. Obtain MRI of the abdomen

IX-30. A 45-year-old man is diagnosed with pheochromocytoma after presentation with confusion, marked hypertension to 250/140, tachycardia, headaches, and flushing. His fractionated plasma metanephrines show a normetanephrine level of 560 pg/mL and a metanephrine level of 198 pg/mL (normal values: normetanephrine, 18–111 pg/mL; metanephrine, 12–60 pg/mL). CT scanning of the abdomen with IV contrast demonstrates a 3-cm mass in the right adrenal gland. A brain MRI with gadolinium shows edema of the white matter near the parieto-occipital junction consistent with reversible posterior leukoencephalopathy. You are asked to consult regarding management. Which of the following statements is true regarding management of pheochromocytoma in this individual?

A. β-Blockade is absolutely contraindicated for tachycardia even after adequate α-blockade has been attained.
B. Immediate surgical removal of the mass is indicated, because the patient presented with hypertensive crisis with encephalopathy.
C. Salt and fluid intake should be restricted to prevent further exacerbation of the patient's hypertension.
D. Phenoxybenzamine should be started at a low dose and titrated to the maximum tolerated dose over 2–3 weeks. Surgery should not be planned until the blood pressure is consistently below 160/100.
E. IV phentolamine is indicated for treatment of the hypertensive crisis.

IX-31. Which of the following is the most common clinical feature of multiple endocrine neoplasia type 1?

A. Carcinoid tumor
B. Gastrinoma
C. Pancreatic islet cell tumor
D. Pheochromocytoma
E. Primary hyperparathyroidism

IX-32. You are seeing a 35-year-old man who last year had a partial thyroidectomy for medullary thyroid carcinoma. You note that he was recently in the hospital and diagnosed with a pheochromocytoma, and after 2 weeks of intensive medical therapy, he underwent unilateral adrenalectomy. He is recovering nicely. You are reviewing his chart before the visit, when you note that on the pathology from his thyroid surgery last year, a single parathyroid gland was removed that was shown to be a parathyroid tumor. When you meet with the patient, you will tell him which of the following?

A. "Family and genetic screening for similar cancers is not useful because the mutations causing these cancers are certainly unrelated and spontaneously arise."
B. "I suspect you have a syndrome called multiple endocrine neoplasia type 1."
C. "I suspect you have a syndrome called multiple endocrine neoplasia type 2."
D. "The partial thyroidectomy was an appropriate treatment for this condition."
E. "These tumors were likely caused by a mutation in the Menin gene."

IX-33. A 35-year-old woman presents to the clinic with fatigue, hair loss, and constipation. She has a history of type 1 diabetes mellitus that is well controlled on insulin and celiac disease, which she manages with a gluten-free diet. On physical examination she has dry skin but no other obvious abnormalities. On laboratory studies, her thyroid-stimulating hormone level is 85 mU/L and thyroid peroxidase antibodies are elevated. What is her underlying syndrome?

A. Autoimmune polyendocrine syndrome type 1 (APS-1)
B. APS-2
C. Immune dysregulation, polyendocrinopathy, enteropathy, and X-linked disease
D. Polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes

IX-34. A 60-year-old man presents to the emergency department with numbness and weakness in his legs and feet. On examination, you find that he is numb to the knees and has marked weakness in ankle dorsiflexion and plantar flexion. Two years ago, he developed diabetes, and last year, he was admitted when found to be profoundly hypothyroid. On examination, he has hepatosplenomegaly and appears to have a dark tan despite having no sun exposure recently. Which of the following tests will likely help make his diagnosis?

A. Anti-nuclear antibody titer measurement
B. Antithymoglobulin antibody titer measurement
C. Blood cultures
D. Serum protein electrophoresis
E. Skin biopsy searching for intravascular clonal T cells

IX-35. An infant is noted to have ambiguous genitalia at birth. The baby has fused labia with clitoral enlargement. The karyotype is 46 XX. The baby has increased levels of 17-hydroxyprogesterone on laboratory studies. Which of the following biochemical abnormalities may be seen?

A. Elevated cortisol
B. Hyperglycemia
C. Hypernatremia
D. Hypokalemia
E. Hyponatremia

IX-36. Patients who have a 46 XY karyotype with complete androgen insensitivity syndrome may have which of the following?

A. Inguinal hernia containing testes
B. No increased risk of gonadal malignancy
C. Primary amenorrhea
D. Uterus
E. A and C

IX-37. A 37-year-old man is evaluated for infertility. He and his wife have been attempting to conceive a child for the past 2 years without success. He initially saw an infertility specialist but was referred to endocrinology after sperm analysis showed no sperm. He is otherwise healthy and only takes a multivitamin. On physical examination, his vital signs are normal. He is tall and has small testes, gynecomastia, and minimal facial and axillary hair. Chromosomal analysis confirms Klinefelter syndrome. Which of the following statements is true?

A. Androgen supplementation is of little use in this condition.
B. He is not at increased risk for breast tumors.
C. Increased plasma concentrations of estrogen are present.
D. Most cases are diagnosed before puberty.
E. Plasma concentrations of follicle-stimulating hormone and luteinizing hormone are decreased in this condition.

IX-38. A 17-year-old teenager is evaluated in your office for primary amenorrhea. She does not feel as if she has entered puberty because she has never had a menstrual period and has sparse axillary and pubic hair growth. On examination, she is noted to be 150 cm tall. She has a low hairline and slight webbing of her neck. Her follicle-stimulating hormone level is 75 mIU/mL, luteinizing hormone level is 20 mIU/mL, and estradiol level is 2 pg/ mL. You suspect Turner syndrome. All of the following tests are indicated in this individual EXCEPT:

A. Buccal smear for nuclear heterochromatin (Barr body)
B. Echocardiogram
C. Karyotype analysis
D. Renal ultrasound
E. Thyroid-stimulating hormone level

IX-39. A 75-year-old man presents to the clinic with several symptomatic complaints. He has been having difficulty with his sexual function. He has issues with erectile function and sexual desire. He has also been more depressed, fatigued, and feels that his thinking is not as sharp as when he was younger. He is also not able to walk as far as previously or play singles tennis. You test his total testosterone level and it is 200 ng/dL (low). Which of his symptoms will be expected to be most improved with the addition of supplemental testosterone?

A. Cognitive function
B. Depression
C. Erectile function
D. Fatigue
E. Physical mobility

IX-40. All of the following cause testicular dysfunction by decreasing levels of testosterone EXCEPT:

A. Alcohol
B. Cirrhosis
C. Ketoconazole
D. Marijuana
E. Radiation therapy during adolescence

IX-41. A 58-year-old man is seen in his primary care physician's office for evaluation of bilateral breast enlargement. This has been present for several months and is accompanied by mild pain in both breasts. He reports no other symptoms. His other medical conditions include coronary artery disease with a history of congestive heart failure, atrial fibrillation, obesity, and type 2 diabetes mellitus. His current medications include lisinopril, spironolactone, furosemide, insulin, and digoxin. He denies illicit drug use and has fathered three children. Examination confirms bilateral breast enlargement with palpable glandular tissue that measures 2 cm bilaterally. Which of the following statements regarding his gynecomastia is true?

A. He should be referred for mammography to rule out breast cancer.
B. His gynecomastia is most likely due to obesity, with adipose tissue present in the breast.
C. Serum testosterone, luteinizing hormone, and follicle-stimulating hormone levels should be measured to evaluate for androgen insensitivity.
D. Spironolactone should be discontinued, and he should be followed for regression.
E. Liver function testing should be performed to screen for cirrhosis.

IX-42. In the menstrual cycle, which of the following hormones is secreted preovulation as a result of estrogen-induced *positive* feedback?

A. Cortisol
B. Follicle-stimulating hormone
C. Gonadotropin-releasing hormone
D. Luteinizing hormone
E. Thyroid-stimulating hormone

IX-43. Which of the following events occurs first in the majority of girls with normal pubertal development?

A. Achieving peak height velocity
B. Breast development
C. Development of axillary hair
D. Development of pubic hair
E. Menarche

IX-44. A 22-year-old woman presents to the clinic with acute onset of severe lower abdominal pain. It started 2 days prior and is worse when she rides over speed bumps in her car. She has also noted some chills at night, but has not taken her temperature. She has some new foul-smelling vaginal discharge but no vaginal bleeding since her last menstrual period (3 weeks prior). She has no prior medical history. She is sexually active with men and uses condoms intermittently. She does not have an intrauterine device or use other forms of contraception. Physical examination shows diffuse tenderness in the lower abdomen but no point tenderness or rebound tenderness. Urine β-human chorionic gonadotropin test is negative. Which of the following is the most likely cause of her pelvic pain?

A. Appendicitis
B. Ectopic pregnancy
C. Endometriosis
D. Fibroids
E. Pelvic inflammatory disease

IX-45. A 28-year-old woman seeks evaluation for secondary amenorrhea. She had a normal menarche at age 14 with regular monthly periods lasting 5–6 days for the last 13 years. Over the last year, she's noticed greater irregularity and has had no menses for the last 6 months. She takes no medications and is sexually active with one partner using condoms as prophylaxis. Her physical examination is notable for normal vital signs, a body mass index of 29 kg/m^2, normal breast development, and normal pelvic examination. Laboratory testing reveals a negative β-human chorionic gonadotropin, normal testosterone, normal dehydroepiandrosterone sulfate, elevated prolactin, and reduced follicle-stimulating hormone. Based on this information, which of the following is the most likely diagnosis?

A. Androgen insensitivity syndrome
B. Neuroendocrine tumor
C. Polycystic ovary syndrome
D. Pregnancy
E. Premature menopause

IX-46. You are evaluating a 23-year-old woman with heavy uterine bleeding. She reports menarche at age 13 with regular monthly 5- to 6-day menses until the age of 19. Starting at age 20, she began having three to four menses per year lasting only 3 days. For the last year, she has had four episodes of heavy uterine bleeding lasting 6–8 days. She has not had any menstruation for 9 months and is not sexually active. She has been diagnosed with type 2 diabetes and takes metformin. On examination, she is mildly hirsute, her blood pressure is 130/85 with heart rate of 85 beats/min and respiratory rate of 14 breaths/min. Her body mass index is 25 kg/m^2 and her SaO_2 on room air is 98%. Her β-human chorionic gonadotropin is negative, testosterone is elevated, and vaginal ultrasound reveals polycystic ovaries. Which of the following is the most effective treatment for her uterine bleeding?

A. Clomiphene
B. Letrozole
C. Prednisone
D. Progesterone
E. Testosterone

IX-47. Which of the following is a cause of hirsutism (androgen-dependent excessive male-pattern hair growth) in women?

A. Addison disease
B. Growth hormone deficiency
C. Hypothyroidism
D. Menopause
E. Polycystic ovarian syndrome

IX-48. A 19-year-old white woman complains of worsening excess hairiness and is worried that she will be mocked as she starts college. She notes increasingly noticeable hair on her upper lip, chin, and arms. She takes no medications and reports a history of irregular menses. On examination, she has normal vital signs, and you note small to medium tufts of dark hair in the areas she mentioned plus in the midline above and below the umbilicus, along the inner thigh, and in the upper and lower back. All of the statements regarding her condition are true EXCEPT:

A. Further hormonal evaluation is likely necessary.
B. She likely has elevated androgen levels.
C. She meets the diagnostic criteria for hirsutism.
D. The most common cause of her condition is congenital adrenal hyperplasia.
E. This condition affects approximately 10% of women.

IX-49. Which of the following are the main hormonal changes that signal menopause as opposed to the perimenopause period?

A. Follicle-stimulating hormone (FSH) decreases, estradiol rises
B. FSH decreases, luteinizing (LH) rises
C. FSH rises, estradiol decreases
D. LH decreases, estradiol decreases
E. LH rises, estradiol rises

IX-50. The Women's Health Initiative study investigated hormonal therapy in post-menopausal women. The study was stopped early due to increased risk of which of the following diseases in the estrogen-only arm?

A. Deep venous thrombosis
B. Endometrial cancer
C. Myocardial infarction
D. Osteoporosis
E. Stroke

IX-51. Which of the following forms of contraception has the highest actual effectiveness at preventing pregnancy?

A. Diaphragm
B. Oral contraceptives with combined estrogen and progesterone
C. Progestin-containing intrauterine device
D. Spermicide
E. Withdrawal method

IX-52. A 38-year-old woman presents to the clinic to discuss contraception options. She has a history of mild hypertension that is well controlled on amlodipine 5 mg daily. She smokes about one pack of cigarettes per day. Her family history is notable for ovarian cancer in her grandmother and a stroke in her father. Which of the following is an *absolute* contraindication for oral contraceptives?

A. Age >35 combined with cigarette use
B. Family history of ovarian cancer
C. Family history of stroke
D. Hypertension

IX-53. A couple that has been married for 5 years has been attempting to conceive a child for the last 12 months. Despite regular intercourse, they have not achieved pregnancy. They are both 32 years of age and have no medical problems. Neither partner is taking medications. Which of the following is the most common cause of this couple's infertility?

A. Endometriosis
B. Male causes
C. Ovulatory dysfunction
D. Tubal defect
E. Unexplained

IX-54. A couple seeks advice regarding infertility. The female partner is 35 years old. She has never been pregnant and was taking oral contraceptive pills from age 20 until age 34. It is now 16 months since she discontinued her oral contraceptives. She is having menstrual cycles approximately once every 35 days, but occasionally will go as long as 60 days between cycles. Most months, she develops breast tenderness about 2–3 weeks after the start of her menstrual cycle. When she was in college, she was treated for *Neisseria gonorrhoeae* that was diagnosed when she presented to the student health center with a fever and pelvic pain. She otherwise has no medical history. She works about 60 hours weekly as a corporate attorney and exercises daily. She drinks coffee daily and alcohol at social occasions only. Her body mass index (BMI) is 19.8 kg/m^2. Her husband, who is 39 years old, accompanies her to the evaluation. He also has never had children. He was married previously from the ages of 24 to 28. He and his prior wife attempted to conceive for about 15 months but were unsuccessful. At that time, he was smoking marijuana on a daily basis and attributed their lack of success to his drug use. He has now been completely free of drugs for 9 years. He suffers from hypertension and is treated with lisinopril 10 mg daily. He is not obese (BMI 23.7 kg/m^2). They request evaluation for their infertility and request help with conception. Which of the following statements is true regarding their infertility and likelihood of success in conception?

A. Determination of ovulation is not necessary in the female partner because most of her cycles occur regularly and she develops breast tenderness midcycle, indicating ovulation.
B. Lisinopril should be discontinued immediately because of the risk of birth defects associated with its use.
C. The female partner should be assessed for tubal patency by a hysterosalpingogram. If significant scarring is found, in vitro fertilization should be strongly considered to decrease the risk of ectopic pregnancy.
D. The prolonged use of oral contraceptives for >10 years has increased the risk of anovulation and infertility.
E. The use of marijuana by the male partner is directly toxic to sperm motility, and this is the likely cause of their infertility.

IX-55. All of the following drugs have been associated with erectile dysfunction EXCEPT:

A. Cimetidine
B. Lithium
C. Metformin
D. Selective serotonin reuptake inhibitors
E. Spironolactone

IX-56. A 62-year-old man comes to the clinic with his spouse complaining of erectile dysfunction. He has a 10-year history of moderately controlled diabetes mellitus and uses insulin. Over the last year, despite intact libido, he has been unable to attain or sustain an erection when attempting sexual intercourse with his wife. He reports that over this time he no longer awakes with an erection as he did previously. Serum chemistries are normal, hemoglobin A1c is 5.8%, and serum testosterone is normal for his age. Which class of drug is most likely to improve his ability to achieve and maintain erection?

A. 5α-Reductase inhibitor
B. Androgen
C. Corticosteroid
D. Phosphodiesterase-5 inhibitor
E. Selective serotonin reuptake inhibitor

IX-57. A 54-year-old woman complains of difficulty having sex because of pain during intercourse. These symptoms began about 8 years ago but have worsened over the last year. She has one sexual partner and is on no medications. Which of the following is most likely to improve her symptoms?

A. Anastrozole
B. Estrogen cream
C. Paroxetine
D. Sildenafil
E. Tamoxifen

IX-58. Which of the following is a more common cause of death for women than for men in the United States?

A. Alzheimer's disease
B. Cancer
C. Cardiovascular disease
D. Diabetes
E. Suicide

IX-59. A 36-year-old woman presents to the clinic to establish primary care. She has a history of hypothyroidism and polycystic ovarian syndrome. She has had two successful pregnancies that were both complicated by gestational hypertension. She also has a family history of stroke in her paternal grandmother and colon cancer in her mother. Which of the following puts her at increased risk for developing type 2 diabetes mellitus?

A. Family history of stroke
B. Gestational hypertension
C. Hypothyroidism
D. Polycystic ovarian syndrome
E. B and D

IX-60. Which of the following statements regarding coronary heart disease (CHD) in women when compared with men is true?

A. Angina is a rare symptom in women with CHD.
B. At the time of diagnosis of CHD, women typically have fewer comorbidities when compared with men.
C. Physicians are less likely to consider CHD in women and are also less likely to recommend both diagnostic and therapeutic procedures in women.
D. Women and men present with CHD at similar ages.
E. Women are more likely to present with ventricular tachycardia, whereas men more commonly have cardiac arrest or cardiogenic shock.

IX-61. Which of the following statements is true regarding sex differences in disease?

A. Most autoimmune diseases are more prevalent in women than men. This is attributed to stimulatory actions of estrogens and the inhibitory actions of androgens on the cellular mediators of immunity, and hormone therapy with oral contraceptives increases the risk of autoimmune disease.
B. Obesity decreases the risk of endometrial cancer in women.
C. Testosterone administered to hypogonadal men will increase the incidence or severity of obstructive sleep apnea. This does not occur with testosterone administered to hypogonadal women.
D. Women are more sensitive to insulin than are men, and thus, women's risk for type 2 diabetes mellitus is lower.
E. Women have a longer QT interval on average than men and are at higher risk for drug-induced torsades de pointes.

IX-62. All of the following findings are associated with low testosterone levels in older men EXCEPT:

A. Decreased muscle mass
B. Dementia
C. Increased risk of coronary artery disease
D. Insulin resistance
E. Higher visceral fat mass

IX-63. Mr. Violet is a 75-year-old man who presents to your clinic reporting worsening urinary symptoms. He has a history of hypertension and takes hydrochlorothiazide (HCTZ). He is a nonsmoker and typically has a glass of sherry before bed. He recently reports increased urinary frequency that awakens him from sleep, a slow stream of urine, and difficulty initiating micturition. Physical examination demonstrates a blood pressure of 125/70 and an enlarged prostate. Prostate-specific antigen is normal. What can be recommended to help his symptoms?

A. Increase fluid intake
B. Initiate finasteride therapy
C. Reduce alcohol intake
D. Take HCTZ in the evening
E. B and C

IX-64. A 29-year-old former competitive power-lifter who stopped competing 6 months earlier due to a deltoid muscle tear confides that he and his wife have been unable to conceive despite over a year of sexual intercourse without contraception. He wonders if there is a "shot or something that can, you know, help me out." You suspect that the patient may be using anabolic-androgenic steroids (AAS). Which of the following statements is true regarding AAS use?

A. AAS users have the same mortality as the general population.
B. An elevated hematocrit should increase suspicion for AAS abuse.
C. Elevated luteinizing hormone levels and suppressed follicle-stimulating hormone levels are clues suggesting AAS abuse.
D. Increased testicular volume is a clue for AAS abuse.
E. Several prolonged clinical trials of AAS abuse have provided the medical community with a sophisticated understanding of the adverse effects of AAS abuse.

IX-65. Which of the following heath conditions is most increased in transgender individuals compared with the general population?

A. Colorectal cancer
B. Heart disease
C. Hypertension
D. Substance abuse disorder
E. Suicide attempt

IX-66. Which of the following is the accurate definition of a patient's "gender identity"?

A. A person's internal sense of their gender
B. How a person defines their own sexuality
C. How a person thinks of their physical or emotional attraction to others
D. Sex assigned at birth

IX-67. A 22-year-old man presents to the clinic with his mother for evaluation of obesity. He has been obese since childhood and has an intellectual disability. He also has short stature and small hands and feet. Testosterone levels are low on laboratory testing. Which of the following is the most likely underlying syndrome?

A. Bardet-Biedl syndrome
B. Cohen syndrome
C. Cushing syndrome
D. Insulinoma
E. Prader-Willi syndrome

IX-68. All of the following health conditions are associated with obesity EXCEPT:

A. Colon cancer
B. Congestive heart failure
C. Hidradenitis suppurativa
D. Knee osteoarthritis
E. Ovarian cancer

IX-69. Which of the following statements regarding the epidemiology of diabetes mellitus is true?

A. Neither type 1 nor type 2 diabetes are increasing worldwide.
B. The prevalence of type 1 and type 2 diabetes is increasing in the United States but not worldwide.
C. The worldwide prevalence of type 1 and type 2 diabetes is increasing.
D. The worldwide prevalence of type 1 diabetes is increasing, but type 2 diabetes is decreasing.
E. The worldwide prevalence of type 2 diabetes is increasing, but type 1 diabetes is decreasing.

IX-70. How commonly are islet cell antibodies found in patients with new-onset type 1 diabetes?

A. 10%
B. 25%
C. 50%
D. 85%
E. 100%

IX-71. A 37-year-old obese woman presents to clinic for routine health evaluation. She reports that over the last year she has had two yeast infections treated with over-the-counter remedies and she frequently feels thirsty. She reports waking up at night to urinate. Which of the following studies is the most appropriate first test in evaluating this patient for diabetes mellitus?

A. Hemoglobin A1c
B. Oral glucose tolerance test
C. Plasma C-peptide level
D. Plasma insulin level
E. Random plasma glucose level

IX-72. Which of the following defines normal glucose tolerance?

A. Fasting plasma glucose <100 mg/dL
B. Fasting plasma glucose <126 mg/dL following an oral glucose challenge
C. Fasting plasma glucose <100 mg/dL, plasma glucose <140 mg/dL following an oral glucose challenge, and hemoglobin A1c <5.6%
D. Hemoglobin A1c <5.6% and fasting plasma glucose <140 mg/dL
E. Hemoglobin A1c <6.0%

IX-73. You have admitted an 18-year-old patient to the adult medical intensive care unit for diabetic ketoacidosis (DKA). The patient was not known previously to be diabetic, but her mother notes that she had been "going to the bathroom a lot" recently and that "she had been really thirsty." The patient's body mass index is 44 kg/m^2. There is no family history of diabetes. You successfully treat the patient for her DKA and note that serum anti-glutamic acid decarboxylase antibodies and anti–islet cell antibodies sent on admission are not detected. The patient and her mother want to know what "type" of diabetes she has. You should tell them which of the following?

A. "Due to the young age of onset, you likely have type 1 diabetes."
B. "Due to your presentation with diabetic ketoacidosis, you likely have type 1 diabetes."
C. "I suspect you have maturity-onset diabetes of the young."
D. "You likely have type 2 diabetes mellitus."
E. "I suspect your diabetes was triggered by a virus."

IX-74. Which of the following preparations of insulin has the longest time to onset and the longest duration of action?

A. Aspart
B. Glargine
C. Lispro
D. NPH
E. Regular

IX-75. Which of the following laboratory values is typically seen in hyperglycemic hyperosmolar state and not in diabetic ketoacidosis?

A. Arterial pH >7.3
B. Elevated plasma ketones
C. Osmolality <320 mOsm/mL
D. Serum bicarbonate <15 mEq/L
E. Sodium <135 mEq/L

IX-76. A 57-year-old man with type 2 diabetes has come to the clinic to discuss options in therapy. He is concerned about potential side effects, in particular weight gain. He has a history of myocardial infarction and subsequently lost 40 lb with diet and exercise. His heart function is normal now. He has previously tried metformin but did not tolerate it due to diarrhea and nausea. He had hypoglycemia with glipizide. Which of the following medications would be best for him to try next?

A. Exenatide
B. Glimepiride
C. Repaglinide
D. Rosiglitazone

IX-77. A 54-year-old woman is diagnosed with type 2 diabetes mellitus after a routine follow-up for impaired fasting glucose showed that her hemoglobin A1c is now 7.6%. She has attempted to lose weight and exercise with no improvement in her hemoglobin A1c, and drug therapy is now recommended. She has mild systemic hypertension that is well controlled and no other medical conditions. Which of the following is the most appropriate first-line therapy?

A. Acarbose
B. Exenatide
C. Glyburide
D. Metformin
E. Sitagliptin

IX-78. A 21-year-old woman with a history of type 1 diabetes mellitus is brought to the emergency department with nausea, vomiting, lethargy, and dehydration. Her mother notes that she stopped taking insulin 1 day before presentation. She is lethargic, has dry mucous membranes, and is obtunded. Blood pressure is 80/40, and heart rate is 112 beats/min. Heart sounds are normal. Lungs are clear. The abdomen is soft, and there is no organomegaly. She is responsive and oriented but diffusely weak. Serum sodium is 126 mEq/L, potassium is 4.3 mEq/L, magnesium is 1.2 mEq/L, blood urea nitrogen is 76 mg/dL, creatinine is 2.2 mg/dL, bicarbonate is 10 mEq/L, and chloride is 88 mEq/L. Serum glucose is 720 mg/dL. All the following are appropriate management steps EXCEPT:

A. 3% sodium solution
B. Arterial blood gas
C. IV insulin
D. IV potassium
E. IV fluids

IX-79. Which of the following regarding care of the hospitalized diabetic patient is true?

A. General anesthesia leads to insulin sensitization and higher risk for hypoglycemia.
B. A greater degree of hyperglycemia during hospitalization has not been associated with worse infectious outcomes.
C. In clinical trials, strict glycemic control (goal, 81–108 mg/dL) is superior to moderate glycemic control (goal, 140 mg/dL).
D. The initiation of total parenteral nutrition is associated with increased insulin requirements.
E. In critically ill patients, subcutaneous insulin is invariably preferred over IV insulin.

IX-80. A 74-year-old man presents with severe pain in his right thigh. This came on suddenly about a few weeks ago. He also notes some weakness in the right leg when trying to climb stairs. He has poorly controlled type 2 diabetes with a hemoglobin A1c of 10%. On examination, he has weakness in his right hip flexors (4/5 on strength testing) but preserved strength elsewhere. Proprioception and pinprick sensation are preserved in the toes. There is no decreased sensation of the thigh. MRI of the lower spine without contrast is unremarkable. Which of the following is the most likely cause of his symptoms?

A. Diabetic amyotrophy
B. Distal symmetric polyneuropathy from diabetes
C. Herniation of a lumbar disk
D. Meralgia paresthetica
E. Vertebral compression fracture

IX-81. Which of the following complications of diabetes mellitus is due to microvascular disease?

A. Cheiroarthropathy
B. Gastroparesis
C. Infections
D. Macular edema
E. Peripheral arterial disease

IX-82. A 55-year-old man with long-standing type 2 diabetes mellitus undergoes an ophthalmologic examination for visual changes. Which of the following is seen on his funduscopic examination (Figure IX-82)?

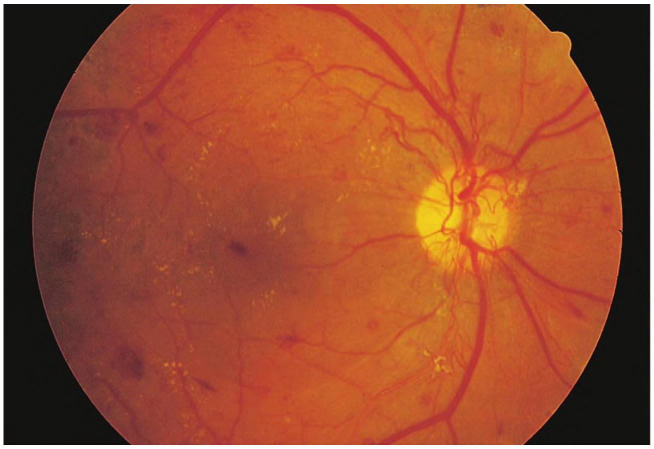


FIGURE IX-82

A. Arteriovenous nicking
B. Microaneurysms
C. Neovascularization
D. Papilledema
E. Retinal detachment

IX-83. Which of the following patients should be treated with either an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker?

A. A 24-year-old woman with type 1 diabetes with two positive spot microalbuminuria tests 1 week apart
B. A 32-year-old woman with type 1 diabetes with a blood glucose of 328 mg/dL and a positive spot microalbuminuria test
C. A 48-year-old man with type 2 diabetes with a positive spot microalbuminuria test 1 week after starting a new exercise program
D. A 56-year-old man with type 2 diabetes with two positive urine spot microalbuminuria tests 3 months apart
E. A 62-year-old man with type 2 diabetes and hypertension with a positive spot microalbuminuria test and a blood pressure on day of testing of 190/118

IX-84. All of the following are risk factors for hypoglycemia in diabetes mellitus EXCEPT:

A. Coronary artery disease
B. Diabetic autonomic neuropathy
C. Impaired renal function
D. Insulin deficiency
E. Lower hemoglobin A1c goal levels

IX-85. Plasma glucose is normally tightly regulated in the body, with fasting levels between 70 and 110 mg/dL. When the blood glucose falls below 80–85 mg/dL, which of the following physiologic changes is the first to occur?

A. Decrease in growth hormone
B. Decrease in insulin secretion
C. Increase in cortisol
D. Increase in epinephrine
E. Increase in glucagon

IX-86. A 25-year-old health care worker is seen for evaluation of recurrent hypoglycemia. She has had several episodes at work over the past year in which she feels shaky, anxious, and sweaty; she measures her fingerstick glucose, and it is 40–55 mg/dL. This has been confirmed with a plasma glucose level during one episode of 50 mg/dL. She then drinks orange juice and feels better. These episodes have not happened outside the work environment. Aside from oral contraceptives, she takes no medications and is otherwise healthy. Which of the following tests is most likely to demonstrate the underlying cause of her hypoglycemia?

A. Measurement of insulin-like growth factor-1
B. Measurement of fasting insulin and glucose levels
C. Measurement of fasting insulin, glucose, and C-peptide levels
D. Measurement of insulin, glucose, and C-peptide levels during a symptomatic episode
E. Measurement of plasma cortisol

IX-87. Which of the following conditions leads to *reduced* levels of low-density lipoprotein cholesterol?

A. Anorexia nervosa
B. Cholestasis
C. Hypothyroidism
D. Nephrotic syndrome
E. Severe liver disease

IX-88. A 70-year-old man with a history of previous myocardial infarction presents for a clinic appointment to discuss his cholesterol-lowering therapy. He has tried both rosuvastatin and pravastatin but had to stop them due to transaminitis and myalgias. His low-density lipoprotein (LDL) cholesterol level is 225 mg/dL off medications. Which of the following is a medication that will lower LDL cholesterol the most, reduce his risk of future cardiovascular events, and not raise triglyceride levels when used as monotherapy?

A. Cholestyramine
B. Evolocumab
C. Ezetimibe
D. Gemfibrozil
E. Omega-3 fatty acids

IX-89. An 18-year-old man presents with severe mid-abdominal pain radiating to his back. Physical examination reveals a temperature of 38.0°C (100.4°F), blood pressure of 95/55, heart rate of 110 beats/min, and respiratory rate of 18 breaths/min, with a room air oxygen saturation of 96%. His abdomen is diffusely tender with voluntary guarding and no rebound tenderness. There is enlargement of the liver and spleen. He also has eruptive xanthomas on his hands, feet, and legs. His lipase is 2300 U/L, and he has a fasting triglyceride level of 1019 mg/dL. After appropriate evaluation, he is presumed to have pancreatitis and lipoprotein lipase deficiency. He stabilizes without complication and is ready for discharge after 4 days. Which of the following do you recommend for treatment?

A. Dietary fat restriction 15 g/d
B. Fish oil supplementation
C. Gemfibrozil 600 mg bid
D. Nicotinic acid sustained-release 250 mg bid
E. Simvastatin 20 mg daily

IX-90. A 32-year-old man is evaluated at a routine clinic visit for coronary risk factors. He reports no tobacco use, his systemic blood pressure is normal, and he does not have diabetes. He is otherwise healthy. His family history is notable for high cholesterol in his mother and maternal grandfather and grandmother. Physical examination shows tendon xanthomas. A fasting lipid panel is notable for a low-density lipoprotein cholesterol level of 387 mg/dL. Which of the following is the most likely genetic disorder affecting this individual?

A. Apolipoprotein (apo) A-V deficiency
B. Familial defective apoB-100
C. Familial hepatic lipase deficiency
D. Familial hypercholesterolemia
E. Lipoprotein lipase deficiency

IX-91. Patients with metabolic syndrome are at higher risk for all of the following EXCEPT:

A. Alzheimer's disease
B. Gout
C. Nonalcoholic fatty liver disease
D. Obstructive sleep apnea
E. Polycystic ovarian syndrome

IX-92. Metabolic syndrome was defined initially as a clinical entity by the World Health Organization in 1998 as a constellation of findings including central obesity, hypertriglyceridemia, low high-density lipoprotein, hyperglycemia, and hypertension. Which of the following statements regarding the epidemiology of metabolic syndrome is true?

A. After the age of 60, men are more likely to have metabolic syndrome than women.
B. Among patients with diabetes mellitus, the presence of metabolic syndrome confers a higher risk of cardiovascular disease.
C. Body mass index is the strongest predictor of insulin resistance and diabetes risk in metabolic syndrome.
D. The highest recorded prevalence of metabolic syndrome in the United States is among Mexican American women.
E. The nationality at the lowest risk of metabolic syndrome is the Japanese population.

IX-93. Which of the following molecules directly activates osteoclast progenitors leading to increased bone resorption and is a target of an osteoporosis treatment drug?

A. Fibroblast growth factor 2
B. Insulin-like growth factor-1
C. Parathyroid hormone
D. RANK ligand
E. Vitamin D

IX-94. All of the following are causes of hypomagnesemia EXCEPT:

A. Diarrhea
B. Ethanol ingestion
C. Hypothyroidism
D. Intestinal malabsorption
E. Vitamin D deficiency

IX-95. A 55-year-old man is admitted to the intensive care unit with 1 week of fever and cough. He was well until 1 week before admission, when he noted progressive shortness of breath, cough, and productive sputum. On the day of admission, the patient was noted by his wife to be lethargic. Emergency response medics found the patient unresponsive. He was intubated in the field and brought to the emergency department. His only medications are insulin glargine 20 units daily and insulin aspart with meals. The past medical history is notable for alcohol abuse and diabetes mellitus. His recent alcohol use has been at least 12 beers daily. On arrival to the hospital, his temperature is 38.9°C (102°F), blood pressure is 76/40, and oxygen saturation is 86% on ventilator setting of assist control, with a tidal volume of 420 mL, respiratory rate of 22 breaths/min, positive end-expiratory pressure of 5, and FiO_2 of 1.0. On examination, the patient is intubated on mechanical ventilation. Jugular venous pressure is normal. There are decreased breath sounds at the right lung base with egophony. Heart sounds are normal. The abdomen is soft. There is no peripheral edema. Chest radiography shows a right lower lobe infiltrate with a moderate pleural effusion. An electrocardiogram is normal. Sputum Gram stain shows gram-positive diplococci. White blood cell count is 23,000/μL, with 70% polymorphonuclear cells and 6% bands. Blood urea nitrogen is 80 mg/dL, and creatinine is 3.1 mg/dL. Plasma glucose is 425 mg/dL. He is started on broad-spectrum antibiotics, IV fluids, omeprazole, and an insulin drip. A nasogastric tube is inserted, and tube feedings are started. On hospital day 2, his creatinine has improved to 1.6 mg/dL. However, plasma phosphate is 1.0 mg/dL (0.3 mmol/L), and calcium is 8.8 mg/dL. All of following are causes of hypophosphatemia is this patient EXCEPT:

A. Acute kidney injury
B. Alcoholism
C. Insulin
D. Malnutrition
E. Sepsis

IX-96. In the patient described in question IX-95, which of the following is the most appropriate approach to correcting his hypophosphatemia?

A. Administer IV calcium gluconate 1 g followed by infusion of IV phosphate at a rate of 8 mmol/h for 6 hours.
B. Administer IV phosphate alone at a rate of 2 mmol/ h for 6 hours.
C. Administer IV phosphate alone at a rate of 8 mmol/ h for 6 hours.
D. Continued close observation as redistribution of phosphate is expected to normalize levels over the course of the next 24–48 hours.
E. Initiate oral phosphate replacement at a dose of 1500 mg/d.

IX-97. You are caring for a 72-year-old man who has been living in a nursing home for the past 3 years. He has severe chronic obstructive pulmonary disease and requires continuous oxygen at 3 L/min. He also previously had a stroke, which has left him with a right hemiparesis. His current medications include aspirin, losartan, hydrochlorothiazide, fluticasone/salmeterol, tiotropium, and albuterol. His body mass index is 18.5 kg/m^2. You are concerned that he may have vitamin D deficiency. Which of the following is the best test to determine whether vitamin D deficiency is present?

A. 1,25-Hydroxy vitamin D
B. 25-Hydroxy vitamin D
C. Alkaline phosphatase
D. Parathyroid hormone
E. Serum total and ionized calcium levels

IX-98. A 72-year-old woman was hospitalized with a right hip fracture. After initial surgical repair, she is transferred to rehabilitation for further care. While there, she has a 25-hydroxyvitamin D level checked, and it returns at 18.3 ng/L (normal >20 ng/L). What do you recommend for treatment in this patient?

A. Vitamin D_3 800 units daily
B. Vitamin D_3 800 units daily plus calcium carbonate 1500 mg daily
C. Vitamin D_3 2000 units daily
D. Vitamin D_3 2000 units daily plus calcium carbonate 1500 mg daily
E. Vitamin D_3 50,000 units weekly for 4 weeks, then 800 units weekly, plus calcium 1500 mg daily

IX-99. A 66-year-old woman presents to discuss her bone densitometry test, which showed Z-scores of –2.9 in the total hip and –3.1 in the lumbar spine. Which of the following laboratory findings would suggest a secondary cause for her low bone density?

A. Decreased morning cortisol level
B. Elevated parathyroid hormone
C. Elevated urine calcium
D. Increased thyroid-stimulating hormone
E. B and C

IX-100. Your patient is a 55-year-old post-menopausal woman. She has normal bone mass on bone densitometry testing. Her 25-OH-vitamin D level is 42 ng/mL (normal) on laboratory testing. Which of the following is the recommended daily intake of calcium and vitamin D?

A. 500 mg calcium, 400 IU vitamin D
B. 500 mg calcium, 1000 IU vitamin D
C. 1200 mg calcium, 400 IU vitamin D
D. 1200 mg calcium, 2000 IU vitamin D
E. 1800 mg calcium, 400 IU vitamin D

IX-101. Which of the following statements regarding the epidemiology of osteoporosis and bone fractures is correct?

A. For every 5-year age increase after age 70, the incidence of hip fractures increases by 25%.
B. Fractures of the distal radius increase in frequency before age 50 and plateau by age 60, with only a modest age-related increase.
C. Most women meet the diagnostic criteria for osteoporosis between the ages of 60 and 70.
D. The risk of hip fracture is equal when white women are compared with black women.
E. Women outnumber men with osteoporosis at a ratio of about 10 to 1.

IX-102. A 50-year-old woman presents to your office to inquire about her risk of fracture related to osteoporosis. She has a positive family history of osteoporosis in her mother, but her mother never experienced any hip or vertebral fractures. The patient herself has also not experienced any fractures. She is white and has a 20 pack-year history of tobacco use, quitting 10 years prior. At the age of 37, she had a total hysterectomy with bilateral salpingo-oophorectomy for endometriosis. She is lactose intolerant and does not consume dairy products. She currently takes calcium carbonate 500 mg daily. Her weight is 115 lb, and her height is 66 in (body mass index 18.6 kg/m^2). All of the following are risk factors for an osteoporotic fracture in this woman EXCEPT:

A. Early menopause
B. Female sex
C. History of cigarette smoking
D. Low body weight
E. Low calcium intake

IX-103. A 45-year-old white woman seeks advice from her primary care physician regarding her risk for osteoporosis and the need for bone density screening. She is a lifelong nonsmoker and drinks alcohol only socially. She has a history of moderate-persistent asthma since adolescence. She is currently on fluticasone, 44 mg/puff twice daily, with good control currently. She last required oral prednisone therapy about 6 months ago when she had influenza that was complicated by an asthma flare. She took prednisone for a total of 14 days. She has had three pregnancies and two live births at ages 39 and 41. She currently has irregular periods occurring approximately every 42 days. Her follicle-stimulating hormone level is 25 mIU/L and

17-β-estradiol level is 115 pg/ mL on day 12 of her menstrual cycle. Her mother and maternal aunt both have been diagnosed with osteoporosis. Her mother also has rheumatoid arthritis and requires prednisone therapy, 5 mg daily. Her mother developed a compression fracture of the lumbar spine at age 68. On physical examination, the patient appears well and healthy. Her height is 168 cm. Her weight is 66.4 kg. The chest, cardiac, abdominal, muscular, and neurologic examinations are normal. Which of the following do you tell the patient about the need for bone density screening?

A. Because she is currently perimenopausal, she should have a bone density screen every other year until she completes menopause and then have bone densitometry measured yearly thereafter.
B. Because of her family history, she should initiate bone density screening yearly beginning now.
C. Bone densitometry screening is not recommended until after completion of menopause.
D. Delayed childbearing until the fourth and fifth decade decreases her risk of developing osteoporosis, so bone densitometry is not recommended.
E. Her use of low-dose inhaled glucocorticoids increases her risk of osteoporosis threefold, and she should undergo yearly bone density screening.

IX-104 to IX-108. Match the following medications used for osteoporosis to the mechanism of action:

IX-104. Calcitonin

IX-105. Denosumab

IX-106. Raloxifene

IX-107. Teriparatide

IX-108. Zoledronic acid

A. Recombinant parathyroid hormone (1-34hPTH) with direct stimulation of osteoblast activity
B. Polypeptide hormone that suppresses osteoclast activity through a specific receptor for the hormone
C. Bisphosphonate drug given on an annual basis that impairs osteoclast function and reduces osteoclast number
D. Selective estrogen receptor modulator
E. Human monoclonal antibody to RANKL

IX-109. A 65-year-old man presents to the clinic with right groin pain that has worsened over the last 6 months. A radiograph of the hip shows coarsening of the trabecular pattern with cortical thickening in the femur (Figure IX-109). Which of the following is the underlying cause of the patient's pain?

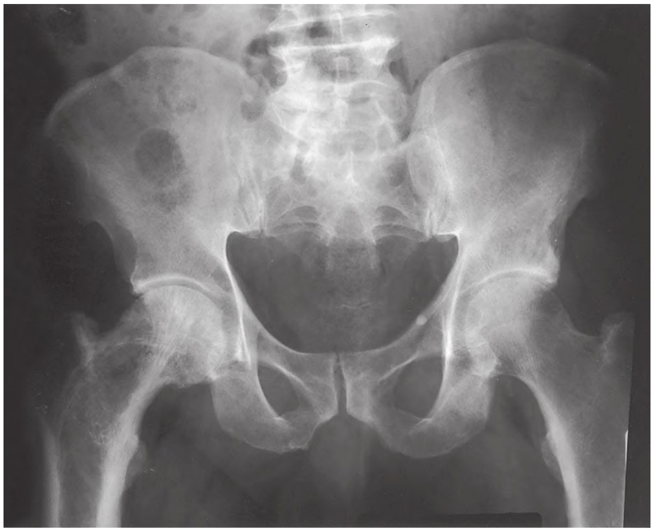


FIGURE IX-109

A. Avascular necrosis
B. Fracture of the femoral neck
C. Paget disease and secondary osteoarthritis
D. Trochanteric bursitis

IX-110. All of the following features can be seen in forms of Ehlers-Danlos syndrome EXCEPT:

A. Congenital hip dislocation
B. Hypermobile joints
C. Lens dislocation
D. Premature loss of teeth
E. Skin hyperextensibility

IX-111. A 19-year-old woman is evaluated by her primary care physician for recurrent long bone fractures. She has fractured her femur twice and her humerus three times. She has not had an abnormal number of falls but does report having easy bruising. Aside from these repeated orthopedic injuries, she is otherwise healthy. Physical examination shows mildly disfigured bones, small, amber-yellowish teeth, and bluish-colored sclera. Osteogenesis imperfecta is suspected. Which of the following statements is true regarding this condition?

A. A mutation in type 1 procollagen likely is present in this patient.
B. Bone biopsy is needed for definitive diagnosis.
C. Bisphosphonates have shown long-term success in preventing long bone fractures in this condition.
D. Fractures in females tend to increase after puberty.
E. Increased bone mineral density may be demonstrated on x-ray absorptiometry.

IX-112. A 20-year-old man is evaluated during a routine physical examination prior to playing for a college basketball team. He was recruited to play on the team and offered a scholarship after being noticed for his skills on a junior national team abroad. He is originally from Nigeria and has come to the United States only for his education. His medical history is significant for prior treatment for tuberculosis at the age of 13. He takes no medications and has no allergies. His father died of sudden cardiac death at the age of 46. No autopsy was performed. Other family members in his father's family have died at young ages from cardiac conditions. His mother is healthy. His height is 79 inches (200.6 cm). His weight is 198 lb (89.8 kg). His body mass index is 22.3 kg/m^2. You note that his torso is short relative to his limbs. His arm span measures 83 inches. He also has pectus excavatum and arachnodactyly. A high-arched palate is present. He wears glasses for severe myopia and has had ectopia lentis on the right. On cardiovascular examination, a II/VI blowing diastolic murmur is noted in the third left intercostal space. He is anxious to begin practicing with the basketball team. What do you advise at this time?

A. He is not safe for further competitive basketball or other strenuous physical activities.
B. He is safe to resume physical activity without further evaluation.
C. He may continue to practice with the team while further evaluation with an echocardiogram, slit-lamp examination, and genetic testing is performed.
D. He should be placed on a beta blocker and then can resume physical activity.

IX-113. All of the following may be required in the treatment of hemochromatosis EXCEPT:

A. Deferoxamine
B. Elimination of alcohol consumption
C. Testosterone replacement
D. Vitamin C supplementation
E. Weekly phlebotomy

IX-114. A 40-year-old man is evaluated as part of an executive physical examination. He has read about different screening procedures on the Internet and is interested in being screened for hemochromatosis. He is otherwise healthy and takes only a daily multivitamin. His father died of cirrhosis at the age of 56 and also drank alcohol heavily. There is no other liver disease in his family. Which of the following tests is the most appropriate first step to screen for this disorder?

A. Genetic testing for C282Y mutation
B. HFE activity assay
C. Liver MRI
D. Screening for hemochromatosis is not cost effective and not advised
E. Transferrin saturation and serum ferritin

IX-115. A 55-year-old white male with a history of diabetes presents to your office with complaints of generalized weakness, weight loss, nonspecific diffuse abdominal pain, and erectile dysfunction. The patient has a past history of hypercholesterolemia and takes atorvastatin. The examination is significant for hepatomegaly without tenderness, testicular atrophy, and gynecomastia. Skin examination shows a diffuse slate-gray hue slightly more pronounced on the face and neck. Joint examination shows mild swelling of the second and third metacarpophalangeal joints on the right hand. Which of the following studies is most likely to lead to the correct diagnosis?

A. Anti–smooth muscle antibody
B. Ceruloplasmin
C. Hepatic ultrasound with Doppler imaging
D. Hepatitis B surface antibody
E. HFE gene mutation screen

IX-116. Which of the following nonhepatic clinical presentations can occur in Wilson disease?

A. Hemolytic anemia
B. Loss of emotional control and sexual disinhibition
C. Proximal muscle weakness
D. Sensory neuropathy
E. A and B

IX-117. A 28-year-old man is admitted to the intensive care unit with fulminant hepatic failure and hemolysis. On further questioning, his family reports that he has been diagnosed with depression for 5 years and had a prior episode of acute hepatitis 2 years ago that resolved. At that time, his aspartate aminotransferase peaked at 1200 U/L and alanine aminotransferase peaked at 1900 U/L. He had only mild jaundice, with a total bilirubin of 7.2 g/dL. No cause of the hepatitis was found despite a workup that included viral and autoimmune causes. His liver function returned to normal. He is taking an antidepressant and occasional ibuprofen, but no other medications. Physical examination is notable for ascites and altered mental status with dystonia. Abdominal CT scan shows no biliary obstruction but a cirrhotic liver. Which of the following findings would be most likely to confirm the underlying diagnosis?

A. 24-Hour urine level of iron
B. Brain MRI showing damage to the basal ganglia
C. Genotype for HFE mutation
D. Schistocytes on peripheral blood smear
E. Slit-lamp ocular examination showing Kayser-Fleischer rings

IX-118. Which of the following is the most appropriate initial treatment for the patient described in question IX-117?

A. Cholestyramine
B. d-Penicillamine
C. Liver transplantation
D. Trientine
E. Zinc

IX-119. A 20-year-old woman is admitted to the hospital for severe intermittent abdominal pain. She has been experiencing similar episodes over the last four years, starting about a year after menarche. She notes that when the attacks of abdominal pain occur her urine looks darker than usual. The abdominal pain is accompanied by vomiting, hypertension, and tachycardia. She also has paresthesias of her arms and legs and new weakness in her left leg. CT of the abdomen with IV and oral contrast shows no acute abnormalities. Which of the following is likely to be found on laboratory testing?

A. Decreased alpha-1 antitrypsin levels
B. Decreased fibrinogen
C. Elevated ferritin
D. Elevated serum copper levels
E. Elevated urine porphyrins

IX-120. A 39-year-old man comes to the clinic complaining of blistering skin lesions on the backs of his hands and arms that are painful. They are often precipitated by sunlight and heal with scarring. He also notices that they often occur after drinking alcohol heavily. His hands and forearms have numerous hypopigmented scars that he says are from previous episodes. The skin over the back of his hands appears thick and coarse. Otherwise his review of systems and physical examination are normal. The lesions on his hands are shown in Figure IX-120. Testing confirms your suspected diagnosis. Which of the following treatments will most likely lead to long-term improvement for this patient?

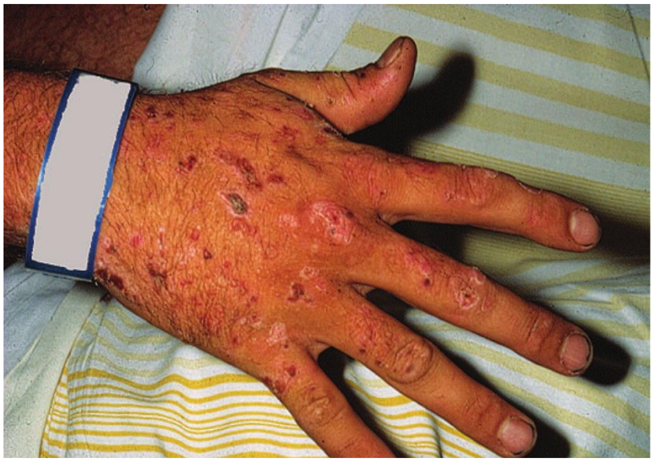


FIGURE IX-120 Used with permission from Dr. Karl E. Anderson.

A. Avoidance of sun exposure and IV hemin for treatment of acute lesions
B. Hydroxychloroquine 200 mg twice daily
C. Phlebotomy of 450 mL of blood every 1–2 weeks
D. Prednisone 0.5 mg/kg orally daily
E. Triamcinolone 0.5% topically twice daily

IX-121. A 25-year-old man of Ashkenazi Jewish ancestry presents to the clinic with new onset, severe right-sided groin pain. On further history, he reports pain in his lower back that has gotten worse over the last several months. He has pain with passive and active external and internal rotation of the hip on examination and vertebral point tenderness at L4-L5. An enlarged spleen is also appreciated on physical examination. Radiographs show necrosis of the femoral head and several vertebral compression fractures. Laboratory studies show a normocytic anemia with no evidence of hemolysis. Which of the following is the most likely diagnosis?

A. Cystic fibrosis
B. Gaucher disease type 1
C. Fabry disease
D. Sickle cell anemia
E. Tay-Sachs Disease

IX-122. A 28-year-old woman is admitted to the hospital with worsening weakness and orthopnea. Over the last 6 months, she has noted difficulty rising from a seated position and in reaching her arms over her head to style her hair. She also finds it difficult to stand up straight; her partner has commented that her posture appears worsened. She has needed to sleep with an extra pillow due to shortness of breath when she lays flat. On examination, she has diminished strength in the deltoids and hip flexors. There are no skin rashes, no spasticity, and no fasciculations of the muscles. Reflexes are normal, and there are no sensory abnormalities. Laboratory studies show a creatinine kinase two times the upper limit of normal. C-reactive protein is normal. Muscle biopsy shows vacuoles that stain positive for glycogen. Which of the following is the underlying cause of her weakness?

A. Amyotrophic lateral sclerosis
B. Chronic fatigue syndrome
C. Dermatomyositis
D. Guillain-Barré syndrome
E. Pompe disease (acid α-1,4 glucosidase deficiency)

IX-123. A 27-year-old man presents to the clinic for management of recurrent flank pain and hematuria. He notices that these symptoms are most likely to present in the summer or when he goes on extended camping trips with limited access to fluid. Serum uric acid is less than 6 mg/dL (normal). Radiographs are unrevealing, but abdominal CT shows multiple stones in the renal pelvis and the bladder. When given a strainer for his urine, several stones are collected. The crystals are hexagonal in an acidified sample of urine. Which of the following is the likely composition of the renal stones?

A. Calcium carbonate
B. Calcium oxalate
C. Cystine
D. Struvite (magnesium ammonium phosphate)
E. Uric acid

ANSWERS

IX-1. **The answer is C.** *(Chap. 371)* The pituitary gland weighs ~600 mg and is located within the sella turcica ventral to the diaphragma sella; it consists of anatomically and functionally distinct anterior and posterior lobes. The bony sella is contiguous to vascular and neurologic structures, including the cavernous sinuses, cranial nerves, and optic chiasm (Figure IX-1). Thus, expanding intrasellar pathologic processes may have significant central mass effects in addition to the endocrinologic impact. The posterior pituitary is supplied by the inferior hypophyseal arteries. In contrast to the anterior pituitary, the posterior lobe is directly innervated by hypothalamic neurons (supraopticohypophyseal and tuberohypophyseal nerve tracts) via the pituitary stalk. Thus, posterior pituitary production of vasopressin (antidiuretic hormone) and oxytocin is particularly sensitive to neuronal damage by lesions that affect the pituitary stalk or hypothalamus.

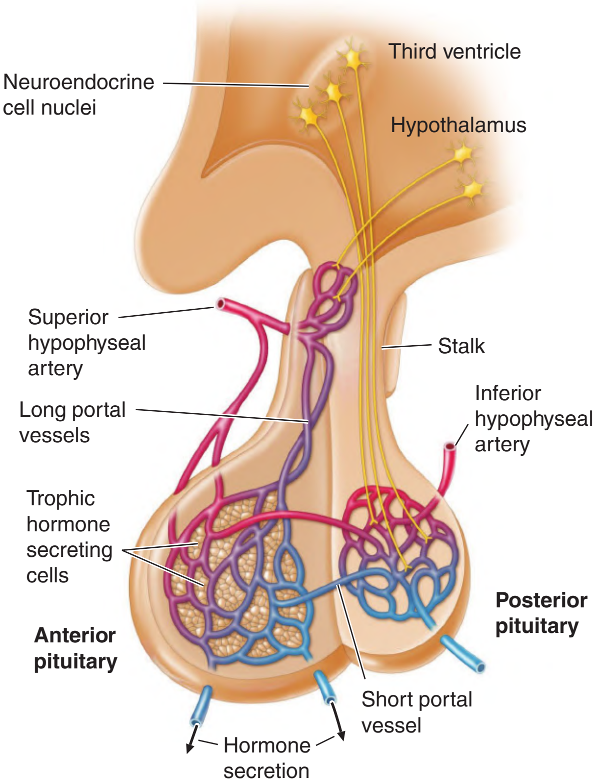

Third ventricle
Neuroendocrine cell nuclei
Hypothalamus
Superior hypophyseal artery
Stalk
Long portal vessels
Inferior hypophyseal artery
Trophic hormone secreting cells
Posterior pituitary
Anterior pituitary
Short portal vessel
Hormone secretion

FIGURE IX-1 Diagram of hypothalamic-pituitary vasculature. The hypothalamic nuclei produce hormones that traverse the portal system and impinge on anterior pituitary cells to regulate pituitary hormone secretion. Posterior pituitary hormones are derived from direct neural extensions.

IX-2. **The answer is C.** *(Chap. 371)* Prolactin (PRL) acts to induce and maintain lactation, decrease reproductive function, and suppress sexual drive. These functions are geared toward ensuring that maternal lactation is sustained and not interrupted by pregnancy. PRL inhibits reproductive function by suppressing hypothalamic gonadotropin-releasing hormone and pituitary gonadotropin secretion and by impairing gonadal steroidogenesis in both women and men. In the ovary, PRL blocks folliculogenesis and inhibits granulosa cell aromatase activity, leading to hypoestrogenism and anovulation. PRL also has a luteolytic effect, generating a shortened, or inadequate, luteal phase of the menstrual cycle.

IX-3. The answer is D. *(Chap. 371)* Functional pituitary adenoma presentations include acromegaly (as in this patient), prolactinomas, or Cushing syndrome. Hypersecretion of growth hormone underlies this syndrome in patients with pituitary masses, although ectopic production of growth hormone, particularly by tumors, has been reported. Because growth hormone is secreted in a highly pulsatile fashion, obtaining random serum levels is not reliable. Thus, the downstream mediator of systemic effects of growth hormone, insulin-like growth factor-1 (IGF-1), is measured to screen for growth hormone excess. IGF-1 is made by the liver in response to growth hormone stimulation. An oral glucose tolerance test with growth hormone obtained at 0, 30, and 60 minutes may also be used to screen for acromegaly because normal persons should suppress growth hormone to this challenge. Serum prolactin level is useful to screen for prolactinomas, and 24-hour urinary free cortisol and adrenocorticotropic hormone assay are useful screens for Cushing disease.

IX-4. The answer is E. *(Chap. 371)* The patient has a clinical presentation consistent with Cushing syndrome. Although many cases of inappropriate elevation of adrenocorticotropic hormone (ACTH) are due to pituitary tumors, a substantial proportion are due to ectopic ACTH secretion. Clues to this diagnosis include a rapid onset of hypercortisolism features associated with skin hyperpigmentation and severe myopathy. Additionally, hypertension, hypokalemic metabolic alkalosis, glucose intolerance, and edema are more prominent in ectopic ACTH secretion than in pituitary tumors. Serum potassium <3.3 mmol/L is present in 70% of patients with ectopic ACTH, but <10% of patients with pituitary-dependent Cushing syndrome. ACTH levels will be high, because this is the underlying cause of both types of Cushing syndrome. Corticotropin-releasing hormone is rarely the cause of Cushing syndrome. Unfortunately, MRI of the pituitary gland will not visualize lesions <2 mm; thus occasionally, sampling of the inferior petrosal veins is required, but this is not yet indicated in this patient at this point in the evaluation.

IX-5. The answer is E. *(Chap. 372)* Hypopituitarism may be caused by accidental or neurosurgical trauma; vascular events such as apoplexy; pituitary or hypothalamic neoplasms, craniopharyngioma, lymphoma, or metastatic tumors; inflammatory disease such as lymphocytic hypophysitis; autoimmune hypophysitis associated with checkpoint inhibitor cancer immunotherapy; infiltrative disorders such as sarcoidosis, hemochromatosis, and tuberculosis; or irradiation. Systemic lupus erythematosus is not known to cause inflammation of the pituitary or hypopituitarism. Increasing evidence suggests that patients with brain injury, including contact sports trauma, subarachnoid hemorrhage, and irradiation, have transient hypopituitarism and require intermittent long-term endocrine follow-up, because permanent hypothalamic or pituitary dysfunction will develop in 25–40% of these patients. These disorders—including sarcoidosis, histiocytosis X, amyloidosis, and hemochromatosis—frequently involve both hypothalamic and pituitary neuronal and neurochemical tracts. Consequently, diabetes insipidus occurs in half of patients with these disorders. Growth retardation is seen if attenuated growth hormone secretion occurs before puberty. Hypogonadotropic hypogonadism and hyperprolactinemia are also common. Pituitary cells express cytotoxic T-lymphocyte antigen-4 (CTLA-4) and up to 20% of patients receiving cancer immunotherapy with CTLA-4 blockers (e.g., ipilimumab) may develop hypophysitis with associated thyroid adrenal and gonadal failure. Pituitary hormone replacement, with or without high-dose glucocorticoids, may be safely tolerated with continued immunotherapy.

IX-6. The answer is C. *(Chap. 372)* Kallmann syndrome results from defective hypothalamic gonadotropin-releasing hormone (GnRH) synthesis and is associated with anosmia or hyposmia due to olfactory bulb agenesis or hypoplasia. Classically, the syndrome may also be associated with color blindness, optic atrophy, nerve deafness, cleft palate, renal abnormalities, cryptorchidism, and neurologic abnormalities such as mirror movements. Associated clinical features, in addition to GnRH deficiency, vary depending on the genetic cause. GnRH deficiency prevents progression through puberty. Males present with delayed puberty and pronounced hypogonadal features, including micropenis, probably the result of low testosterone levels during infancy. Females present with primary amenorrhea and failure of secondary sexual development. Long-term treatment of males with human chorionic gonadotropin or testosterone restores pubertal development and secondary sex characteristics; women can be treated with cyclic estrogen and progestin. Fertility may be restored by the administration of gonadotropins or by using a portable infusion pump to deliver subcutaneous, pulsatile GnRH.

IX-7. **The answer is B.** *(Chap. 372)* This patient has evidence of Sheehan syndrome after giving birth. In this syndrome, the postpartum hyperplastic pituitary is at increased risk for hemorrhage and/or infarction. This leads to bilateral visual changes, headache, and meningeal signs. Ophthalmoplegia may be observed. In severe cases, cardiovascular collapse and altered levels of consciousness may be observed. Laboratory evaluation commonly shows hypoglycemia. Pituitary CT or MRI may show signs of sellar hemorrhage if present. Involvement of all pituitary hormones may be seen, although the most acute findings are often hypoglycemia and hypotension from failure of adrenocorticotropic hormone. The hypoglycemia and hypotension present in this patient suggest failure of the glucocorticoid system; thus treatment with a corticosteroid is indicated. There is no evidence of sepsis; thus antibiotics and drotrecogin alfa are not indicated. With a normal hematocrit and no reported evidence of massive hemorrhage, packed red cell transfusion is unlikely to be helpful. Although thyroid-stimulating hormone production is undoubtedly low in this patient, the most immediate concern is replacement of glucocorticoid.

IX-8. **The answer is B.** *(Chap. 372)* Cranial irradiation may result in long-term hypothalamic and pituitary dysfunction, especially in children and adolescents, because they are more susceptible to damage after whole-brain or head and neck therapeutic irradiation. The development of hormonal abnormalities correlates strongly with irradiation dosage and the time interval after completion of radiotherapy. Up to two-thirds of patients ultimately develop hormone insufficiency after a median dose of 50 Gy (5000 rad) directed at the skull base. The development of hypopituitarism occurs over 5–15 years and usually reflects hypothalamic damage rather than primary destruction of pituitary cells. Although the pattern of hormone loss is variable, growth hormone deficiency is most common, followed by gonadotropin and adrenocorticotropic hormone deficiency. When deficiency of one or more hormones is documented, the possibility of diminished reserve of other hormones is likely. Accordingly, anterior pituitary function should be continually evaluated over the long term in previously irradiated patients, and replacement therapy should be instituted when appropriate.

IX-9. **The answer is B.** *(Chap. 372)* The identification of an empty sella is often an incidental MRI finding. Typically, these patients will have normal pituitary function and should be reassured. It is likely that the surrounding rim of pituitary tissue is functioning normally. An empty sella may signal the insidious onset of hypopituitarism, and laboratory results should be followed closely. Unless her clinical situation changes, repeat MRI is not indicated. Endocrine malignancy is unlikely, and surgery is not part of the management of an empty sella.

IX-10. **The answer is D.** *(Chap. 373)* The presenting clinical features of functional pituitary adenomas (e.g., acromegaly, prolactinomas, or Cushing syndrome) should guide the laboratory studies. However, for a sellar mass with no obvious clinical features of hormone excess, laboratory studies are geared toward determining the nature of the tumor and assessing the possible presence of hypopituitarism. When a pituitary adenoma is suspected based on MRI, initial hormonal evaluation usually includes (1) basal prolactin; (2) insulin-like growth factor-1; (3) 24-hour urinary free cortisol and/or overnight oral dexamethasone (1 mg) suppression test; (4) α-subunit, follicle-stimulating hormone, and luteinizing hormone; and (5) thyroid function tests.

IX-11. **The answer is E.** *(Chap. 373)* Diagnosing functional pituitary adenomas requires combining screening tests (Table IX-11) and imaging. Pituitary gland height ranges from 6 mm in children to 8 mm in adults; during pregnancy and puberty, the height may reach 10–12 mm. The upper aspect of the adult pituitary is flat or slightly concave, but in

TABLE IX-11 Screening Tests for Functional Pituitary Adenomas

	Test	Comments
Acromegaly	Serum IGF-1 Oral glucose tolerance test with GH obtained at 0, 30, and 60 min	Interpret IGF-1 relative to age- and sex-matched controls Normal subjects should suppress growth hormone to <1 μ/L
Prolactinoma	Serum PRL	Exclude medications MRI of the sella should be ordered if PRL is elevated
Cushing disease	24-h urinary free cortisol Dexamethasone (1 mg) at 11 PM and fasting plasma cortisol measured at 8 AM ACTH assay	Ensure urine collection is total and accurate Normal subjects suppress to <5 μ/dL Distinguishes adrenal adenoma (ACTH suppressed) from ectopic ACTH or Cushing disease (ACTH normal or elevated)

Abbreviations: ACTH, adrenocorticotropin hormone; GH, growth hormone; IGF-1, insulin-like growth factor-1; MRI, magnetic resonance imaging; PRL, prolactin.

adolescent and pregnant individuals, this surface may be convex, reflecting physiologic pituitary enlargement. The stalk should be midline and vertical. Anterior pituitary gland soft tissue consistency is slightly heterogeneous on MRI, and signal intensity resembles that of brain matter on T1-weighted imaging. Adenoma density is usually lower than that of surrounding normal tissue on T1-weighted imaging, and the signal intensity increases with T2-weighted images. The high phospholipid content of the posterior pituitary results in a pituitary "bright spot."

IX-12. **The answer is C.** *(Chap. 373)* Because optic tracts may be contiguous to an expanding pituitary mass, reproducible visual field assessment using perimetry techniques should be performed on all patients with sellar mass lesions that impinge the optic chiasm. Bitemporal hemianopia, often more pronounced superiorly, is observed classically. It occurs because nasal ganglion cell fibers, which cross in the optic chiasm, are especially vulnerable to compression of the ventral optic chiasm. Occasionally, homonymous hemianopia occurs as a result of postchiasmal compression, or monocular temporal field loss occurs as a result of prechiasmal compression.

IX-13. **The answer is D.** *(Chap. 374)* A decrease of 75% or more in the secretion or action of arginine vasopressin (AVP) usually results in diabetes insipidus (DI), a syndrome characterized by the production of abnormally large volumes of dilute urine (Table IX-13). The 24-hour urine volume exceeds 40 mL/kg body weight, and the osmolarity is <300 mOsm/L. The polyuria produces symptoms of urinary frequency, enuresis, and/or nocturia, which may disturb sleep and cause mild daytime fatigue or somnolence. It also results in a slight rise in plasma osmolarity that stimulates thirst and a commensurate increase in fluid intake (polydipsia). Overt clinical signs of dehydration are uncommon unless thirst and/or the compensatory increase of fluid intake are also impaired. Primary deficiency of AVP secretion usually results from agenesis or irreversible destruction of the neurohypophysis. It is referred to variously as neurohypophyseal DI, neurogenic DI, pituitary DI, cranial DI, or central DI. It can be caused by a variety of congenital, acquired, or genetic disorders, but in about one-half of all adult patients, it is idiopathic. Craniopharyngioma, pituitary surgery, and sarcoid can cause a primary deficiency of AVP secretion. Secondary deficiencies of AVP secretion result from inhibition by excessive intake of fluids. They are referred to as primary polydipsia and can be divided into three subcategories. One of them, dipsogenic DI, is characterized by inappropriate thirst caused by a reduction in the set of the osmoregulatory mechanism. It sometimes occurs in association with multifocal diseases of the brain such as neurosarcoid, tuberculous meningitis, and multiple sclerosis but is often idiopathic. The second subtype, psychogenic polydipsia, is not associated with thirst, and the polydipsia seems to be a feature of psychosis or obsessive compulsive disorder. The third subtype, iatrogenic polydipsia, results from recommendations to increase fluid intake for its presumed health benefits. Primary deficiencies in the antidiuretic action of AVP result in nephrogenic DI. The causes can be genetic, acquired, or drug induced.

TABLE IX-13 Causes of Diabetes Insipidus

Pituitary diabetes insipidus

- Acquired
  - Head trauma (closed and penetrating) including pituitary surgery
  - Neoplasms
    - Primary
      - Craniopharyngioma
      - Pituitary adenoma (suprasellar)
      - Dysgerminoma
      - Meningioma
    - Metastatic (lung, breast)
    - Hematologic (lymphoma, leukemia)
  - Granulomas
    - Sarcoidosis
    - Histiocytosis
    - Xanthoma disseminatum
  - Infectious
    - Chronic meningitis
    - Viral encephalitis
    - Toxoplasmosis
  - Inflammatory
    - Lymphocytic infundibulo-neurohypophysitis
    - Granulomatosis with polyangiitis (Wegener syndrome)
    - Lupus erythematosus
    - Scleroderma
  - Chemical toxins
    - Tetrodotoxin
    - Snake venom
  - Vascular
    - Sheehan syndrome
    - Aneurysm (internal carotid)
    - Aortocoronary bypass
    - Hypoxic encephalopathy
  - Idiopathic
- Congenital malformations
  - Septo-optic dysplasia
  - Midline craniofacial defects
  - Holoprosencephaly
  - Hypogenesis, ectopia of pituitary
- Genetic
  - Autosomal dominant (*AVP-neurophysin* gene)
  - Autosomal recessive
  - Type A (*AVP-neurophysin* gene)
  - Type B (*AVP-neurophysin* gene)
  - Type C (*Wolfram [4p-WFS 1]* gene)
  - X-linked recessive (Xq28)

Gestational diabetes insipidus

- Pregnancy (second and third trimesters)

Nephrogenic diabetes insipidus

- Acquired
  - Drugs
    - Lithium
    - Demeclocycline
    - Methoxyflurane
    - Amphotericin B
    - Aminoglycosides
    - Cisplatin
    - Rifampin
    - Foscarnet
  - Metabolic
    - Hypercalcemia, hypercalciuria
    - Hypokalemia
  - Obstruction (ureter or urethra)
  - Vascular
    - Sickle cell disease and trait
    - Ischemia (acute tubular necrosis)
  - Granulomas
    - Sarcoidosis
  - Neoplasms
    - Sarcoma
  - Infiltration
    - Amyloidosis
  - Idiopathic
- Genetic
  - X-linked recessive (*AVP receptor-2* gene)
  - Autosomal recessive (*AQP2* gene)
  - Autosomal dominant (*AQP2* gene)

Primary polydipsia

- Acquired
  - Psychogenic
    - Schizophrenia
    - Obsessive compulsive disorder
  - Dipsogenic (abnormal thirst)
    - Granulomas (sarcoidosis)
    - Infectious (tuberculous meningitis)
    - Head trauma (closed and penetrating)
    - Demyelination (multiple sclerosis)
    - Drugs
    - Idiopathic
    - Iatrogenic

IX-14. The answer is C. *(Chap. 375)* Iodine deficiency is prevalent in many mountainous regions and in central Africa, central South America, and northern Asia. Europe remains mildly iodine deficient, and health surveys indicate that iodine intake has been falling in the United States and Australia. The World Health Organization estimates that about 2 billion people are iodine deficient, based on urinary excretion data. In areas of relative iodine deficiency, there is an increased prevalence of goiter and, when deficiency is severe, hypothyroidism and cretinism. Cretinism is characterized by mental and growth retardation and occurs when children who live in iodine-deficient regions are not treated with iodine or thyroid hormone to restore normal thyroid hormone levels during early life. These children are often born to mothers with iodine deficiency, and it is likely that maternal thyroid hormone deficiency worsens the condition. Concomitant selenium deficiency may also contribute to the neurologic manifestations of cretinism. Iodine supplementation of salt, bread, and other food substances has markedly reduced the prevalence of cretinism. Unfortunately, however, iodine deficiency remains the most common cause of preventable mental deficiency, often because of societal resistance to food additives or the cost of supplementation. In addition to overt cretinism, mild iodine deficiency can lead to subtle reduction of IQ. Oversupply of iodine, through supplements or foods enriched in iodine (e.g., shellfish, kelp), is associated with an increased incidence of autoimmune thyroid disease. The Recommended Daily Allowance is 220 μg iodine per day for pregnant women and 290 μg iodine per day for breastfeeding women. Because the effects of iodine deficiency are most severe in pregnant women and their babies, the American Thyroid Association has recommended that all pregnant and breastfeeding women in the United States and Canada take a prenatal multivitamin containing 150 μg iodine per day. Urinary iodine is >10 μg/dL in iodine-sufficient populations.

IX-15. The answer is B. *(Chap. 375)* A number of conditions are associated with normal thyroid function but hyperthyroxinemia is not. Although some of these are associated with clinical hyperthyroidism, many have simply elevated levels of total T_4 and normal conversion to triiodothyronine (T_3) and, thus, are clinically normal. Anything that increases liver production of thyroid-binding globulin will produce elevated total T_4 levels and normal free T_4 and T_3 levels. In this category are pregnancy, estrogen-containing oral contraceptives, cirrhosis, and familial excess thyroid-binding globulin production. Familial dysalbuminemic hyperthyroxinemia results in an albumin mutation and increased T_4 with normal free T_4 and T_3 levels. Euthyroid sick syndrome occurs during acute medical and psychiatric illness. In this syndrome, there is transiently increased unbound T_4 and decreased thyroid-stimulating hormone. Total T_4 and T_3 may be decreased, particularly later in the course of disease.

IX-16. The answer is E. *(Chap. 376)* The patient has myxedema coma precipitated by an infection. Myxedema coma still has a 20–40% mortality rate, despite intensive treatment, and outcomes are independent of the T_4 and thyroid-stimulating hormone levels. Clinical manifestations include reduced level of consciousness, sometimes associated with seizures, as well as the other features of hypothyroidism. Hypothermia can reach 23°C (74°F). There may be a history of treated hypothyroidism with poor compliance, or the patient may be previously undiagnosed. Myxedema coma almost always occurs in the elderly and is usually precipitated by factors that impair respiration, such as drugs (especially sedatives, anesthetics, and antidepressants), pneumonia, congestive heart failure, myocardial infarction, gastrointestinal bleeding, or cerebrovascular accidents. Sepsis should also be suspected. Exposure to cold may also be a risk factor. Hypoventilation, leading to hypoxia and hypercapnia, plays a major role in pathogenesis; hypoglycemia and dilutional hyponatremia also contribute to the development of myxedema coma. Levothyroxine can initially be administered as a single IV bolus of 200–400 μg, which serves as a loading dose, followed by a daily oral dose of 1.6 μg/kg per day, reduced by 25% if administered IV. If suitable IV preparation is not available, the same initial dose of levothyroxine can be given by nasogastric tube (although absorption may be impaired in myxedema). Because $T_4 \rightarrow T_3$ conversion is impaired in myxedema coma, there is a rationale for adding liothyronine (T_3) intravenously or via nasogastric tube to levothyroxine treatment, although excess liothyronine has the potential to provoke arrhythmias. Parenteral hydrocortisone (50 mg every 6 hours) should be administered, because there is impaired adrenal reserve in profound hypothyroidism. Any precipitating factors should be treated, including the early use of broad-spectrum antibiotics, pending the exclusion of infection. Ventilatory support with regular blood gas analysis is usually needed during the first 48 hours. Hypertonic saline or IV glucose may be needed if there is severe hyponatremia or hypoglycemia; hypotonic IV fluids should be avoided because they may exacerbate water retention secondary to reduced renal perfusion and inappropriate vasopressin secretion. The metabolism of most medications is impaired, and sedatives should be avoided if possible or used in reduced doses. Medication blood levels should be monitored, when available, to guide dosage.

IX-17. The answer is D. *(Chap. 376)* Secondary hypothyroidism is usually diagnosed in the context of other anterior pituitary hormone deficiencies; isolated thyroid-stimulating hormone (TSH) deficiency is very rare. TSH levels may be low, normal, or even slightly increased in secondary hypothyroidism; the latter is due to secretion of immunoreactive but bio-inactive forms of TSH. The diagnosis is confirmed by detecting a low unbound T_4 level. The goal of treatment is to maintain T_4 levels in the upper half of the reference interval, because TSH levels cannot be used to monitor therapy.

IX-18. **The answer is A.** *(Chap. 376)* There are a number of important effects of thyroid hormone (or its absence) on the cardiovascular system. Importantly, hypothyroidism is associated with bradycardia, reduced myocardial contractility, and thus reduced stroke volume. Increased peripheral resistance may be accompanied by systemic hypertension, particularly diastolic in hypothyroidism. Pericardial effusions are found in up to 30% of patients with hypothyroidism, although they rarely cause decreased cardiac function. Finally, in hypothyroid patients, blood flow is directed away from the skin, thus producing cool extremities.

IX-19. **The answer is A.** *(Chap. 376)* The most common cause of hypothyroidism in the United States is autoimmune thyroiditis, because the United States is an iodine-replete area. Although earlier in the disease, a radioiodine uptake scan may have shown diffusely increased uptake from lymphocytic infiltration, at this point in the disease, when the infiltrate is “burned out,” there is likely to be little found on the scan. Likewise, a thyroid ultrasound would only be useful for presumed multinodular goiter. Antithyroid peroxidase antibodies are commonly found in patients with autoimmune thyroiditis, whereas antithyroglobulin antibodies are found less commonly. Antithyroglobulin antibodies are also found in other thyroid disorders (Graves disease, thyrotoxicosis) as well as systemic autoimmune diseases (systemic lupus erythematosus). Thyroglobulin is released from the thyroid in all types of thyrotoxicosis with the exception of factitious disease. This patient, however, was hypothyroid, and thus serum thyroglobulin levels are unlikely to be helpful.

IX-20. **The answer is D.** *(Chap. 377)* The patient has a classic story for subacute thyroiditis presenting in the thyrotoxic phase. Many viruses have been implicated, including mumps, coxsackie, influenza, adenoviruses, and echoviruses, but attempts to identify the virus in an individual patient are often unsuccessful and do not influence management. The diagnosis of subacute thyroiditis is often overlooked because the symptoms can mimic pharyngitis. The peak incidence occurs at 30–50 years, and women are affected three times more frequently than men. The patient usually presents with a painful and enlarged thyroid, sometimes accompanied by fever. There may be features of thyrotoxicosis or hypothyroidism, depending on the phase of the illness. Malaise and symptoms of an upper respiratory tract infection may precede the thyroid-related features by several weeks. In other patients, the onset is acute, severe, and without obvious antecedent. The patient typically complains of a sore throat, and examination reveals a small goiter that is exquisitely tender. Pain is often referred to the jaw or ear. Complete resolution is the usual outcome, but late-onset permanent hypothyroidism occurs in 15% of cases, particularly in those with coincidental thyroid autoimmunity. A prolonged course over many months, with one or more relapses, occurs in a small percentage of patients. As depicted in Figure IX-20, thyroid function tests characteristically evolve through three distinct phases over about 6 months: (1) thyrotoxic phase, (2) hypothyroid phase, and (3) recovery phase. In the thyrotoxic phase, T_4 and T_3 levels are increased, reflecting their discharge from the damaged thyroid cells, and thyroid-stimulating hormone is suppressed. The T_4/T_3 ratio is greater than in Graves disease or thyroid autonomy, in which T_3 is often disproportionately increased. The diagnosis is confirmed by a high erythrocyte sedimentation rate and low uptake of radioiodine (<5%) or ^{99m}Tc pertechnetate (compared with salivary gland pertechnetate concentration). The white blood cell count may be increased, and thyroid antibodies are negative. If the diagnosis is in doubt, fine-needle aspiration biopsy may be useful, particularly to distinguish unilateral involvement from bleeding into a cyst or neoplasm.

IX-21. **The answer is A.** *(Chap. 377)* Patients with Graves disease produce thyroid-stimulating immunoglobulins. They subsequently produce higher levels of T_4 compared with the normal population. As a result, many patients with Graves disease are mildly iodine deficient, and T_4 production is somewhat limited by the availability of iodine. Exposure to iodinated contrast thus reverses iodine deficiency and may precipitate worsening hyperthyroidism.

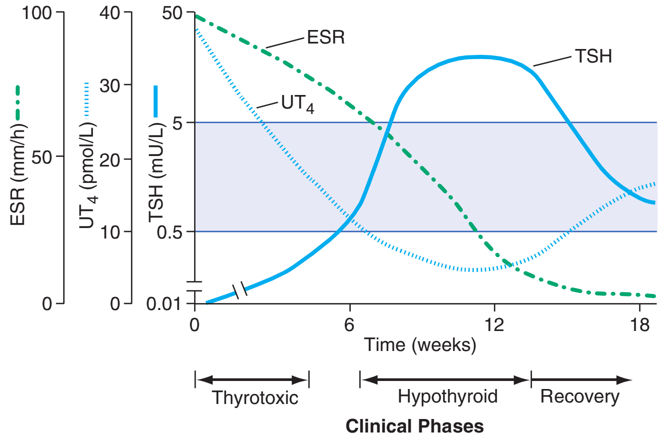


FIGURE IX-20 *Abbreviations:* ESR, erythrocyte sedimentation rate; TSH, thyroid-stimulating hormone; UT_4, unbound T_4.

Additionally, the reversal of mild iodine deficiency may make iodine-125 therapy for Graves disease less successful because thyroid iodine uptake is lessened in the iodine replete state.

IX-22. The answer is A. *(Chap. 378)* An approach to the evaluation of a solitary nodule is outlined in Figure IX-22. Most patients with thyroid nodules have normal thyroid function tests.

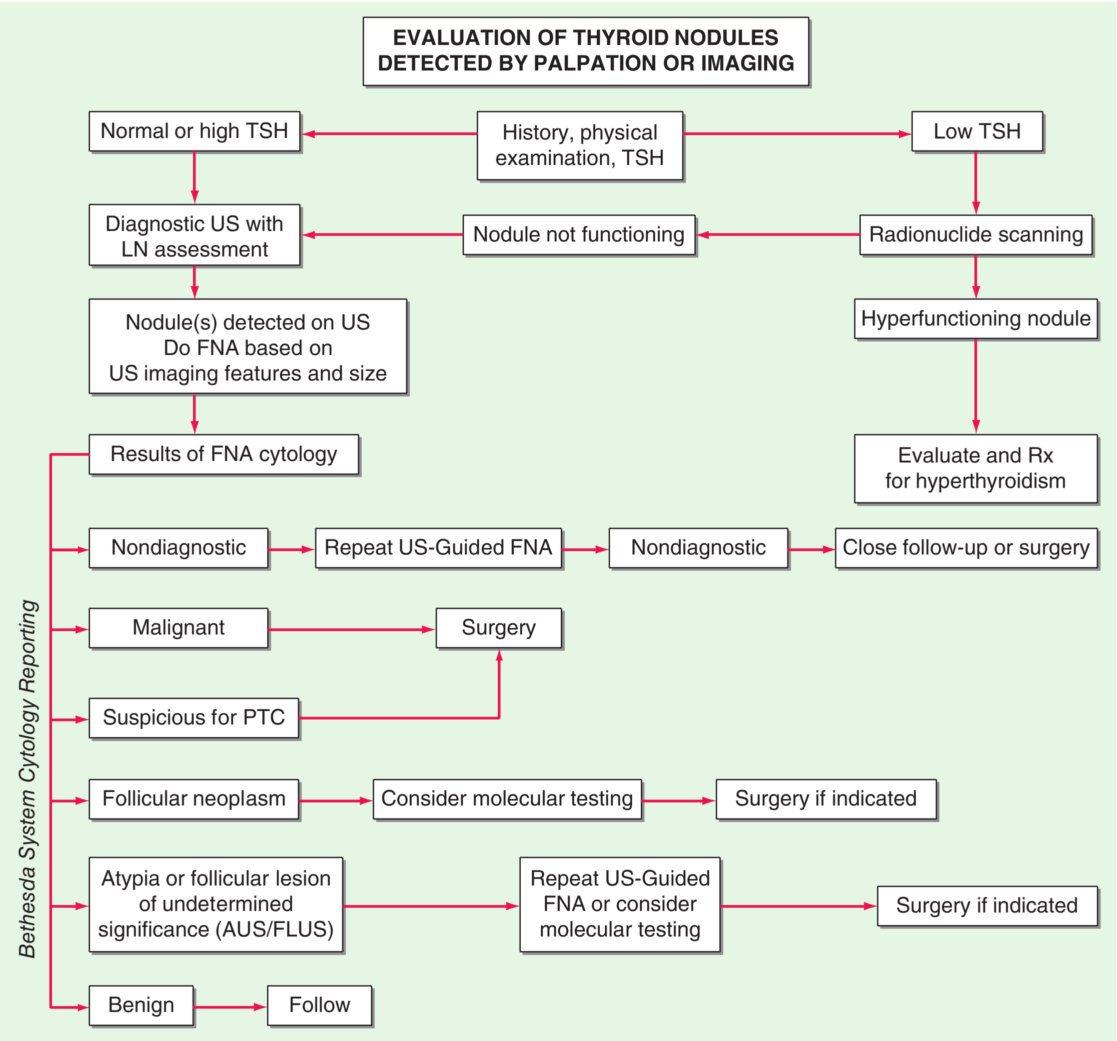

EVALUATION OF THYROID NODULES
DETECTED BY PALPATION OR IMAGING
Normal or high TSH
History, physical examination, TSH
Low TSH
Diagnostic US with LN assessment
Nodule not functioning
Radionuclide scanning
Nodule(s) detected on US Do FNA based on US imaging features and size
Hyperfunctioning nodule
Results of FNA cytology
Evaluate and Rx for hyperthyroidism
Nondiagnostic
Repeat US-Guided FNA
Nondiagnostic
Close follow-up or surgery
Malignant
Surgery
Suspicious for PTC
Follicular neoplasm
Consider molecular testing
Surgery if indicated
Atypia or follicular lesion of undetermined significance (AUS/FLUS)
Repeat US-Guided FNA or consider molecular testing
Surgery if indicated
Benign
Follow
Bethesda System Cytology Reporting

FIGURE IX-22 *Abbreviations:* FNA, fine-needle aspiration; LN, lymph node; PTC, papillary thyroid cancer; TSH, thyroid-stimulating hormone; US, ultrasound.

Nonetheless, thyroid function should be assessed by measuring a thyroid-stimulating hormone (TSH) level, which may be suppressed by one or more autonomously functioning nodules. If the TSH is suppressed, a radionuclide scan is indicated to determine whether the identified nodule is "hot," as lesions with increased uptake are almost never malignant and fine-needle aspiration (FNA) is unnecessary. Otherwise, the next step in evaluation is performance of a thyroid ultrasound for three reasons. (1) Ultrasound will confirm if the palpable nodule is indeed a nodule. About 15% of "palpable" nodules are not confirmed on imaging; therefore, no further evaluation is required. (2) Ultrasound will assess if there are additional nonpalpable nodules for which FNA may be recommended based on imaging features and size. (3) Ultrasound will characterize the imaging pattern of the nodule, which, combined with the nodule's size, facilitates decision-making about FNA. Numerous studies have demonstrated consistent risk estimates for thyroid cancer based on certain sonographic patterns. For example, a spongiform nodule has a <3% chance of cancer and observation rather than FNA is reasonable, whereas 10–20% of solid hypoechoic nodules with smooth borders are malignant and FNA is recommended at a size cutoff of 1 cm. Evidence-based guidelines from both the American Thyroid Association (ATA) and the American Association of Clinical Endocrinologists provide recommendations for nodule FNA based on sonographic patterns and size cutoffs, with lower size cutoffs for nodules with more suspicious ultrasound patterns. Given what is known about the prevalence and generally indolent behavior of small thyroid cancers <1 cm, the 2015 ATA guidelines do not recommend FNA for any nodule <1 cm unless metastatic cervical lymph nodes are present.

IX-23. **The answer is C.** *(Chap. 379)* Incidentally discovered adrenal masses, commonly termed adrenal "incidentalomas," are common, with a prevalence of 2–5% in the general population as documented in CT and autopsy series (Table IX-23). The prevalence increases with age, with 1% of 40-year-olds and 7% of 70-year-olds harboring an adrenal mass. The widespread use of cross-sectional imaging has also increased the recognized prevalence. Most solitary adrenal tumors are monoclonal neoplasms. The majority of adrenal nodules are endocrine-inactive adrenocortical adenomas. However, larger series suggest that up to

TABLE IX-23 Classification of Unilateral Adrenal Masses

Mass	Approximate Prevalence (%)
Benign	
Adrenocortical adenoma	
Endocrine-inactive	60–85
Cortisol-producing	5–10
Aldosterone-producing	2–5
Pheochromocytoma	5–10
Adrenal myelolipoma	<1
Adrenal ganglioneuroma	<0.1
Adrenal hemangioma	<0.1
Adrenal cyst	<1
Adrenal hematoma/hemorrhagic infarction	<1
Indeterminate	
Adrenocortical oncocytoma	<1
Malignant	
Adrenocortical carcinoma	2–5
Malignant pheochromocytoma	<1
Adrenal neuroblastoma	<0.1
Lymphomas (including primary adrenal lymphoma)	<1
Metastases (most frequent: breast, lung)	1–2

Note: Bilateral adrenal enlargement/masses may be caused by congenital adrenal hyperplasia, bilateral macronodular hyperplasia, bilateral hemorrhage (due to antiphospholipid syndrome or sepsis-associated Waterhouse-Friderichsen syndrome), granuloma, amyloidosis, or infiltrative disease including tuberculosis.

25% of adrenal nodules are hormonally active, due to a cortisol- or aldosterone-producing adrenocortical adenoma or a pheochromocytoma associated with catecholamine excess. Adrenocortical carcinoma is rare but is the cause of an adrenal mass in 5% of patients. However, metastases originating from another solid tissue tumor are an additional cause of adrenal incidentaloma, and have a higher incidence in patients undergoing imaging for tumor staging or follow-up monitoring.

IX-24. **The answer is C.** *(Chap. 379)* The early age of hypertension and hypokalemia suggests mineralocorticoid excess. Diagnostic screening for mineralocorticoid excess is not currently recommended for all patients with hypertension, but it should be restricted to those who exhibit hypertension associated with drug resistance, hypokalemia, an adrenal mass, or onset of disease before the age of 40 years (Figure IX-24). The accepted screening test is concurrent measurement of plasma renin and aldosterone with subsequent calculation

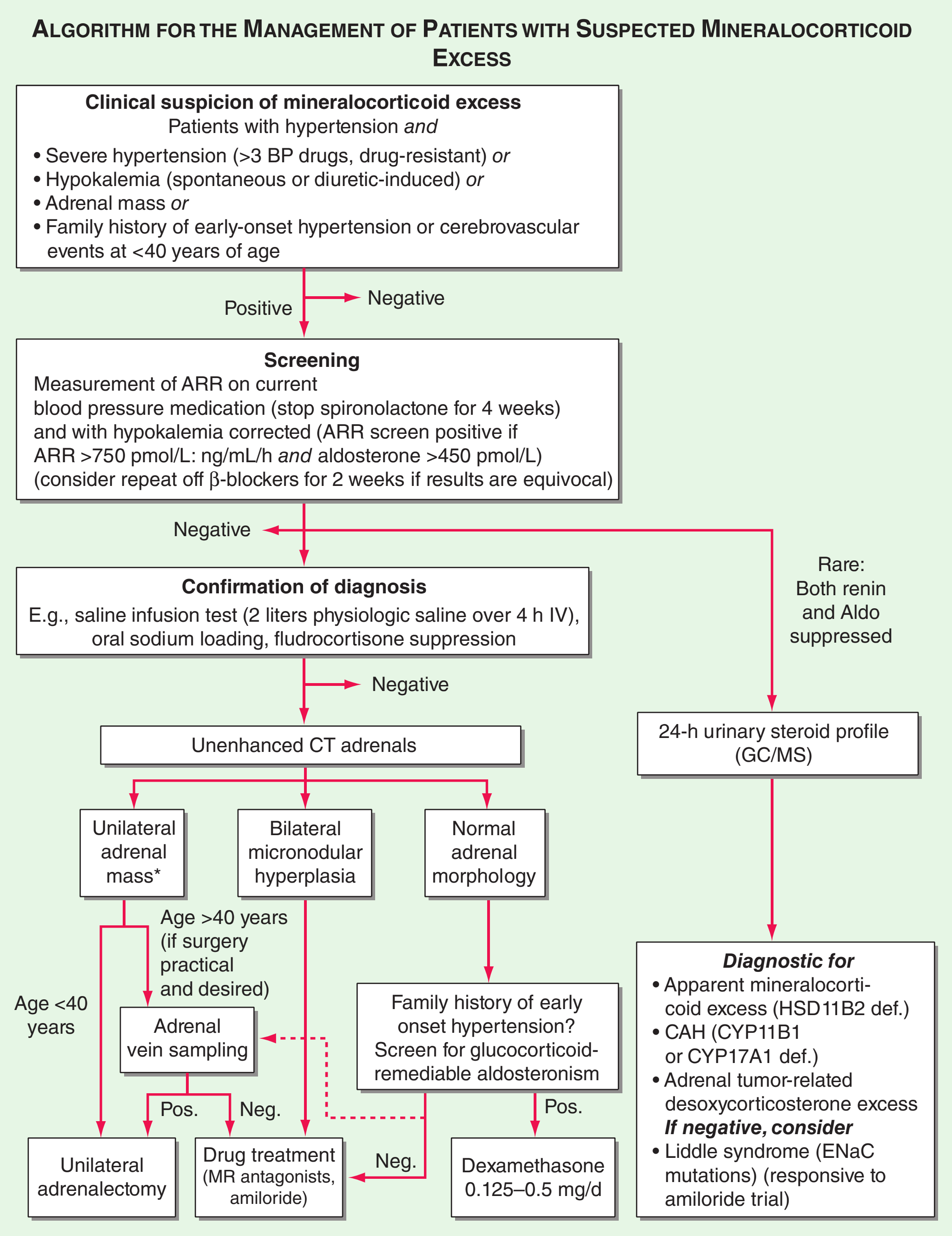

ALGORITHM FOR THE MANAGEMENT OF PATIENTS WITH SUSPECTED MINERALOCORTICOID EXCESS
Clinical suspicion of mineralocorticoid excess
Patients with hypertension and
• Severe hypertension (>3 BP drugs, drug-resistant) or
• Hypokalemia (spontaneous or diuretic-induced) or
• Adrenal mass or
• Family history of early-onset hypertension or cerebrovascular events at <40 years of age
Positive
Negative
Screening
Measurement of ARR on current blood pressure medication (stop spironolactone for 4 weeks) and with hypokalemia corrected (ARR screen positive if ARR >750 pmol/L: ng/mL/h and aldosterone >450 pmol/L) (consider repeat off β-blockers for 2 weeks if results are equivocal)
Negative
Rare: Both renin and Aldo suppressed
Confirmation of diagnosis
E.g., saline infusion test (2 liters physiologic saline over 4 h IV), oral sodium loading, fludrocortisone suppression
Negative
Unenhanced CT adrenals
24-h urinary steroid profile (GC/MS)
Unilateral adrenal mass*
Bilateral micronodular hyperplasia
Normal adrenal morphology
Age >40 years (if surgery practical and desired)
Age <40 years
Adrenal vein sampling
Family history of early onset hypertension? Screen for glucocorticoid-remediable aldosteronism
Diagnostic for
• Apparent mineralocorticoid excess (HSD11B2 def.)
• CAH (CYP11B1 or CYP17A1 def.)
• Adrenal tumor-related desoxycorticosterone excess
If negative, consider
• Liddle syndrome (ENaC mutations) (responsive to amiloride trial)
Pos.
Neg.
Pos.
Neg.
Unilateral adrenalectomy
Drug treatment (MR antagonists, amiloride)
Dexamethasone 0.125–0.5 mg/d

FIGURE IX-24 *Abbreviations:* Aldo, aldosterone; ARR, aldosterone-renin ratio; BP, blood pressure; CAH, congenital adrenal hyperplasia; CT, computed tomography; ENaC, epithelial sodium channel; GC/MS, gas chromatography/mass spectrometry; MR, mineralocorticoid receptor.

of the aldosterone-renin ratio (ARR); serum potassium needs to be normalized prior to testing. ARR screening is positive if the ratio is >750 pmol/L per ng/mL per hour, with a concurrently high normal or increased aldosterone. CT of the adrenals is recommended if ARR is found to be elevated, not before testing. There are no signs of Cushing syndrome or adrenal insufficiency to suggest testing cortisol levels up front. There are no signs in this patient of pheochromocytoma or hyperthyroidism to indicate testing of thyroid-stimulating hormone or metanephrines.

IX-25. **The answer is C.** *(Chap. 379)* The adrenal gland has three major functions: glucocorticoid synthesis, aldosterone synthesis, and androgen precursor synthesis. Glucocorticoid synthesis is controlled by the pituitary secretion of adrenocorticotropic hormone. The primary stimulus for aldosterone synthesis is the renin-angiotensin-aldosterone system, which is independent of the pituitary. Thus, morning cortisol secretion and release of cortisol in response to stress are regulated by the pituitary gland, whereas regulation of sodium retention and potassium excretion by aldosterone is independent of the pituitary and would be preserved in this patient.

IX-26. **The answer is A.** *(Chap. 379)* Cushing syndrome is a constellation of features that result from chronic exposure to elevated levels of cortisol from any etiology. Although the most common etiology is an adrenocorticotropic hormone (ACTH)-producing pituitary adenoma, which accounts for 75% of Cushing syndrome, 15% of cases are due to ectopic ACTH syndromes such as bronchial or pancreatic tumors, small-cell lung cancer, and other causes. ACTH-independent Cushing syndrome is much rarer. Adrenocortical adenoma underlies 5–10% of cases, and adrenocortical carcinoma is present in 1% of Cushing cases. McCune-Albright syndrome is a genetic cause of bone abnormalities, skin lesions (café-au-lait), and premature puberty, particularly in girls. Interestingly, it is caused by a sporadic in utero mutation, not an inherited disorder, and thus will not be passed on to progeny.

IX-27. **The answer is A.** *(Chap. 379)* On examination the patient has central obesity; abdominal stria; broad, purple stretch marks; thin skin; and hyperpigmented knuckles. Often, this is due to exogenous (corticosteroid) administration, although it could also be due to endogenous production (Cushing syndrome). A physiological stressor, such as trauma or infection, may trigger adrenal crisis. Importantly (although not present in this case), hyperthyroidism can also trigger adrenal crisis via increased glucocorticoid inactivation. Thus, stress glucocorticoids must always be provided first in the setting of concomitant thyroid and adrenal insufficiency. Acute adrenal insufficiency requires immediate initiation of rehydration, usually carried out by saline infusion at initial rates of 1 L/h with continuous cardiac monitoring. Glucocorticoid replacement should be initiated by bolus injection of 100 mg of hydrocortisone, followed by the administration of 100–200 mg of hydrocortisone over 24 hours, either by continuous infusion or by bolus IV or IM injections. Mineralocorticoid replacement can be initiated once the daily hydrocortisone dose has been reduced to <50 mg because, at higher doses, hydrocortisone provides sufficient stimulation of mineralocorticoid receptors.

IX-28. **The answer is E.** *(Chap. 380)* About 25–33% of patients with a pheochromocytoma or paraganglioma have an inherited syndrome. At diagnosis, patients with inherited syndromes are a mean of ~15 years younger than patients with sporadic tumors. The best-known pheochromocytoma-associated syndrome is the autosomal dominant disorder multiple endocrine neoplasia (MEN) 2. Both types of MEN 2 (2A and 2B) are caused by mutations in *RET*, which encodes a tyrosine kinase. The locations of *RET* mutations correlate with the severity of disease and the type of MEN 2. MEN 2A is characterized by medullary thyroid carcinoma (MTC), pheochromocytoma, and hyperparathyroidism; MEN 2B also includes MTC and pheochromocytoma as well as multiple mucosal neuromas, marfanoid habitus, and other developmental disorders, though it typically lacks hyperparathyroidism. MTC is found in virtually all patients with MEN 2, but pheochromocytoma occurs in only ~50% of these patients. Nearly all pheochromocytomas in MEN 2 are benign and located in the adrenals, often bilaterally. Pheochromocytoma may be symptomatic before MTC. Prophylactic thyroidectomy is being performed in many carriers of *RET* mutations; pheochromocytomas should be excluded before any surgery in these patients. Von Hippel-Lindau disease (VHL) is an autosomal dominant disorder that predisposes one to retinal and cerebellar hemangioblastomas, which also occur in the brainstem and spinal cord. Dr. William Kaelin's investigations into the molecular mechanisms of VHL disease were recognized with the 2019 Nobel Prize in Medicine or Physiology. Other important features of VHL are clear cell renal carcinomas, pancreatic neuroendocrine tumors, endolymphatic sac tumors of the inner ear, cystadenomas of the epididymis and broad ligament, and multiple pancreatic or renal cysts. Although the *VHL* gene can be inactivated by all types of mutations, patients with pheochromocytoma predominantly have missense mutations. About 20–30% of patients with VHL have pheochromocytomas, but in some families the incidence can reach 90%. MEN 1 and Turner syndrome are not associated with pheochromocytomas.

IX-29. **The answer is A.** *(Chap. 380)* When the diagnosis of pheochromocytoma is entertained, the first step is measurement of catecholamines and/or metanephrines. This can be achieved by urinary tests for vanillylmandelic acid, catecholamines, fractionated metanephrines, or total metanephrines. Testing for total metanephrines has a high sensitivity and, therefore, is frequently used. A value of three times the upper limit of normal is highly suggestive of pheochromocytoma. Borderline elevations, as this patient had, are likely to be false positives. The next most appropriate step is to remove potentially confounding dietary or drug exposures, if possible, and repeat the test. Likely culprit drugs include levodopa, sympathomimetics, diuretics, tricyclic antidepressants, and alpha and beta blockers (labetalol in this case). Sertraline is a selective serotonin reuptake inhibitor antidepressant, not a tricyclic. Alternatively, a clonidine suppression test may be ordered.

IX-30. **The answer is E.** *(Chap. 380)* Complete removal of the pheochromocytoma is the only therapy that leads to a long-term cure, although 90% of tumors are benign. However, preoperative control of hypertension is necessary to prevent surgical complications and lower mortality. This patient is presenting with encephalopathy in a hypertensive crisis. The hypertension should be managed initially with IV medications to lower the mean arterial pressure by approximately 20% over the initial 24-hour period. Medications that can be used for hypertensive crisis in pheochromocytoma include nitroprusside, nicardipine, and phentolamine. Once the acute hypertensive crisis has resolved, transition to oral α-adrenergic blockers is indicated. Phenoxybenzamine is the most commonly used drug and is started at low doses (5–10 mg three times daily) and titrated to the maximum tolerated dose (usually 20–30 mg daily). Once alpha blockers have been initiated, beta blockade can be safely used and is particularly indicated for ongoing tachycardia. Liberal salt and fluid intake helps expand plasma volume and treat orthostatic hypotension. Once blood pressure is maintained below 160/100 with moderate orthostasis, it is safe to proceed to surgery. If blood pressure remains elevated despite treatment with alpha blockade, the addition of calcium channel blockers, angiotensin receptor blockers, or angiotensin-converting enzyme inhibitors should be considered. Diuretics should be avoided because they will exacerbate orthostasis.

IX-31. **The answer is E.** *(Chap. 381)* Multiple endocrine neoplasia type 1 (MEN 1), which is also referred to as Wermer syndrome, is characterized by the triad of tumors involving the parathyroids, pancreatic islets, and anterior pituitary. In addition, adrenal cortical tumors, carcinoid tumors usually of the foregut, meningiomas, facial angiofibromas, collagenomas, and lipomas may also occur in some patients with MEN 1. The prevalence of MEN 1 is ~0.25% based on randomly chosen postmortem studies but is 1–18% among patients with primary hyperparathyroidism, 16–38% among patients with pancreatic islet tumors, and <3% among patients with pituitary tumors. The disorder affects all age groups, with a reported age range of 5–81 years, with clinical and biochemical manifestations developing in the vast majority by the fifth decade.

Primary hyperparathyroidism occurs in ~90% of patients and is the most common feature of MEN 1. Patients may have asymptomatic hypercalcemia or vague symptoms associated with hypercalcemia (e.g., polyuria, polydipsia, constipation, malaise, or dyspepsia).

Nephrolithiasis and osteitis fibrosa cystica (less commonly) may also occur. Biochemical investigations reveal hypercalcemia, usually in association with elevated circulating parathyroid hormone. The incidence of pancreatic islet cell tumors, which are neuroendocrine tumors, in patients with MEN 1 ranges from 30 to 80% in different series. Gastrin-secreting tumors (gastrinomas) are associated with marked gastric acid production and recurrent peptic ulcerations, a combination referred to as the Zollinger-Ellison syndrome. Gastrinomas occur more often in patients with MEN 1 who are aged >30 years. Pheochromocytomas are seen in MEN 2.

IX-32. **The answer is C.** *(Chap. 381)* Multiple endocrine neoplasia type 2 (MEN 2), also called Sipple syndrome, is characterized by the association of medullary thyroid carcinoma (MTC), pheochromocytomas, and parathyroid tumors. In MEN 2A (the most common variant), MTC is associated with pheochromocytomas in 50% of patients (may be bilateral) and with parathyroid tumors in 20% of patients. MEN 1, which is also referred to as Wermer syndrome, is characterized by the triad of tumors involving the parathyroids, pancreatic islets, and anterior pituitary. MEN 1 syndrome is caused by a mutation in the *Menin* (or MEN 1) gene. MEN 2 is caused by a mutation in the *RET* gene. Family and genetic screening both have high value in this syndrome (MEN 2) because prophylactic thyroidectomy, with lifelong thyroxine replacement, has dramatically improved outcomes in patients with MEN 2 and MEN 3, such that approximately 90% of young patients with *RET* mutations who had a prophylactic thyroidectomy have no evidence of persistent or recurrent MTC at 7 years after surgery. Partial thyroidectomy is inappropriate for this patient; in patients with clinically evident MTC, a total thyroidectomy with bilateral central resection is recommended.

IX-33. **The answer is B.** *(Chap. 382)* Autoimmune polyendocrine syndrome type 2 (APS-2; OMIM 269200) is more common than APS-1 with a prevalence of 1–2 in 100,000 (Table IX-33). It has a gender bias and occurs more often in female patients with a ratio of at least 3:1 compared with male patients. In contrast to APS-1, APS-2 often has its onset in adulthood with a peak incidence between 20 and 60 years of age. It shows a familial, multigenerational heritage. The presence of two or more of the following endocrine deficiencies in the same patient defines the presence of APS-2: primary adrenal insufficiency (Addison disease; 50–70%), Graves disease or autoimmune thyroiditis (15–69%), type 1 diabetes mellitus (40–50%), and primary hypogonadism. Frequently associated autoimmune conditions include celiac disease (3–15%), myasthenia gravis, vitiligo, alopecia, serositis, and pernicious anemia. These conditions occur with increased frequency in affected patients, but they are also are found in their family members. APS-1 (OMIM 240300) has also been called autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy. Mucocutaneous candidiasis, hypoparathyroidism, and Addison disease form the three major components of this disorder. Classical APS-1 develops very early in life, often in infancy. Immune dysregulation, polyendocrinopathy, enteropathy, and X-linked

TABLE IX-33 Comparison of APS-1 and APS-2

APS-1	APS-2
Early onset: infancy	Later onset
Siblings often affected and at risk	Multigenerational
Equivalent sex distribution	Females > males affected
Monogenic: *AIRE* gene, chromosome 21, autosomal recessive	Polygenic: *HLA, MICA, PTNP22, CTLA4*
Not HLA associated for entire syndrome, some specific component risk	DR3/DR4 associated; other HLA class III gene associations noted
Autoantibodies to type 1 interferons and IL-17 and IL-22	No autoantibodies to cytokines
Autoantibodies to specific target organs	Autoantibodies to specific target organs
Asplenism	No defined immunodeficiency
Mucocutaneous candidiasis	Association with other nonendocrine immunologic disorders like myasthenia gravis and idiopathic thrombocytopenic purpura

Abbreviations: APS, autoimmune polyendocrine syndrome; HLA, human leukocyte antigen; IL, interleukin.

disease (IPEX) is a rare X-linked recessive disorder. The disease onset is in infancy and is characterized by severe enteropathy, type 1 diabetes, and skin disease, as well as variable association with several other autoimmune disorders. In polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes (POEMS) syndrome, patients usually present with a progressive sensorimotor polyneuropathy, diabetes mellitus (50%), primary gonadal failure (70%), and a plasma cell dyscrasia with sclerotic bony lesions. Associated findings can be hepatosplenomegaly, lymphadenopathy, and hyperpigmentation. Patients often present in the fifth to sixth decade of life and have a median survival after diagnosis of <3 years.

IX-34. **The answer is D.** *(Chap. 382)* This patient likely has polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes (POEMS). Patients usually present with a progressive sensorimotor polyneuropathy, diabetes mellitus (50%), primary gonadal failure (70%), and a plasma cell dyscrasia with sclerotic bony lesions. Associated findings can be hepatosplenomegaly, lymphadenopathy, and hyperpigmentation. Patients often present in the fifth and sixth decades of life and have a median survival after diagnosis of less than 3 years. The detection of an M-protein on serum electrophoresis would make POEMS the most likely diagnosis.

IX-35. **The answer is E.** *(Chap. 383)* The baby has congenital adrenal hyperplasia caused by 21-hydroxylase deficiency. Glucocorticoid insufficiency causes a compensatory elevation of adrenocorticotropic hormone (ACTH), resulting in adrenal hyperplasia and additional synthesis of steroid precursors proximal to the enzymatic block. Increased androgen synthesis in utero causes androgenization of the 46,XX fetus in the first trimester. Ambiguous genitalia are seen at birth, with varying degrees of clitoral enlargement and labial fusion. Excess androgen production causes gonadotropin-independent precocious puberty in males with 21-hydroxylase deficiency (OHD). The *salt-wasting* form of 21-OHD results from severe combined glucocorticoid and mineralocorticoid deficiency. A salt-wasting crisis usually manifests between 5 and 21 days of life and is a potentially life-threatening event that requires urgent fluid resuscitation and steroid treatment. Thus, a diagnosis of 21-OHD should be considered in any baby with atypical genitalia with bilateral nonpalpable gonads. Males (46, XY) with 21-OHD have no genital abnormalities at birth but are equally susceptible to adrenal insufficiency and salt-losing crises. Biochemical features of acute salt-wasting 21-OHD are hyponatremia, hyperkalemia, hypoglycemia, inappropriately low cortisol and aldosterone, and elevated 17-hydroxyprogesterone, ACTH, and plasma renin activity. Presymptomatic diagnosis of classic 21-OHD is now made by neonatal screening tests for increased 17-hydroxyprogesterone in many centers. In most cases, 17-hydroxyprogesterone is markedly increased. In adults, ACTH stimulation (0.25 mg of cosyntropin IV) with assays for 17-hydroxyprogesterone at 0 and 30 minutes can be useful for detecting nonclassic 21-OHD and heterozygotes.

IX-36. **The answer is E.** *(Chap. 383)* Mutations in the androgen receptor cause resistance to androgen (testosterone, dihydrotestosterone) action or the *androgen insensitivity syndrome* (*AIS*). AIS is a spectrum of disorders that affects at least 1 in 100,000 46,XY individuals. Because the androgen receptor is X-linked, only 46,XY offspring are affected if the mother is a carrier of a mutation. XY individuals with complete AIS (CAIS; formerly called *testicular feminization syndrome*) have a female phenotype, normal breast development (due to aromatization of testosterone), a short vagina but no uterus (because Müllerian inhibiting substance [MIS] production is normal), scanty pubic and axillary hair, and a female gender identity and sex role behavior. Gonadotropins and testosterone levels can be low, normal, or elevated, depending on the degree of androgen resistance and the contribution of estradiol to feedback inhibition of the hypothalamic-pituitary-gonadal axis. anti-Müllerian hormone/MIS levels in childhood are normal or high. CAIS sometimes presents as inguinal hernias (containing testes) in childhood or more often with primary amenorrhea in late adolescence. Because there is a low risk of malignancy, gonadectomy has been recommended for girls diagnosed in childhood, with estrogen replacement prescribed at puberty. Alternatively, the gonads can be left in situ until breast development is complete and then removed to avoid tumor risk. Some adults with CAIS decline gonadectomy, but should be counseled about the risk of malignancy, especially because early detection of premalignant changes by imaging or biomarkers is currently not possible.

IX-37. The answer is C. *(Chap. 383)* Klinefelter syndrome is a chromosomal disorder with 47,XXY. Because the primary feature of this disorder is gonadal failure, low testosterone is present, and thus, increased luteinizing hormone (LH) and follicle-stimulating hormone are produced in an attempt to increase testosterone production in the feedback loop of sex hormones. Increased estrogen production is often present because of chronic Leydig cell stimulation by LH and aromatization of androstenedione by adipose tissue. The lower testosterone-to-estrogen ratio results in mild feminization with gynecomastia. Features of low testosterone are small testes and eunuchoid proportions with long legs and incomplete virilization. Biopsy of the testes, although rarely performed, shows hyalinization of the seminiferous tubules and azoospermia. Although severe cases are diagnosed prepubertally as a result of small testes and impaired androgenization, approximately 75% of cases are not diagnosed, and the frequency in the general population is 1 in 1000. Patients with Klinefelter syndrome are at increased risk of breast tumors, thromboembolic disease, learning difficulties, obesity, diabetes mellitus, and varicose veins.

IX-38. The answer is A. *(Chap. 383)* Turner syndrome most frequently results from a 45,X karyotype, but mosaicism (45,X/46,XX) also can result in this disorder. Clinically, Turner syndrome manifests as short stature and primary amenorrhea if presenting in young adulthood. In addition, chronic lymphedema of the hands and feet, nuchal folds, a low hairline, and high-arched palate are also common features. To diagnose Turner syndrome, karyotype analysis should be performed. A Barr body results from inactivation of one of the X chromosomes in women and is not seen in males. In Turner syndrome, the Barr body should be absent, but only 50% of individuals with Turner syndrome have the 45,X karyotype. Thus, the diagnosis could be missed in those with mosaicism or other structural abnormalities of the X chromosome. Multiple comorbid conditions are found in individuals with Turner syndrome, and appropriate screening is recommended. Congenital heart defects affect 30% of women with Turner syndrome, including bicuspid aortic valve, coarctation of the aorta, and aortic root dilatation. An echocardiogram should be performed, and the individual should be assessed with blood pressures in the arms and legs. Hypertension can also be associated with structural abnormalities of the kidney and urinary tract, most commonly horseshoe kidney. A renal ultrasound is also recommended. Autoimmune thyroid disease affects 15–30% of women with Turner syndrome and should be assessed by screening thyroid-stimulating hormone. Other comorbidities that may occur include sensorineural hearing loss, elevated liver function enzymes, osteoporosis, and celiac disease.

IX-39. The answer is C. *(Chap. 384)* Several epidemiologic studies, such as the Framingham Heart Study, the European Male Ageing Study (EMAS), and the Study of Osteoporotic Fractures in Men that used mass spectrometry for measuring testosterone levels have reported ~10% prevalence of low testosterone levels in middle-aged and older men; the prevalence of unequivocally low testosterone and sexual symptoms in men aged 40–70 years in the EMAS was 2.1%, and increased with age from 0.1% for men aged 40–49 years of age to 5.1% for those aged 70–79 years. The age-related decline in testosterone should be distinguished from classical hypogonadism due to diseases of the testes, the pituitary, and the hypothalamus. An analysis of signs and symptoms in older men in the EMAS revealed a syndromic association of sexual symptoms with total testosterone levels below 320 ng/dL and free testosterone levels below 64 pg/mL in community-dwelling older men. A series of placebo-controlled testosterone trials have provided important information about the efficacy of testosterone in improving outcomes in older men. Testosterone replacement in older men, aged ≥65, with sexual symptoms improved sexual activity, sexual desire, and erectile function more than placebo. Testosterone replacement did not improve fatigue or cognitive function, and had only a small effect on mood and mobility. Among older men with low testosterone and age-associated memory impairment, testosterone replacement did not improve memory or other measures of cognition relative to placebo. Testosterone replacement was associated with significantly greater increase in vertebral as well as femoral volumetric bone mineral density and estimated bone strength relative to placebo. Testosterone replacement was associated with a greater increase in hemoglobin levels and corrected anemia in a greater proportion of men who had unexplained anemia of aging.

IX-40. The answer is D. *(Chap. 384)* Drugs can interfere with testicular function by several mechanisms, including inhibition of testosterone synthesis (e.g., ketoconazole) blockade of androgen action (e.g., spironolactone), increased estrogen (e.g., marijuana), or direct inhibition of spermatogenesis (e.g., chemotherapy). Marijuana does not inhibit testosterone synthesis as opposed to ketoconazole, which does. Alcohol, when consumed in excess for prolonged periods, decreases testosterone, independent of liver disease or malnutrition. Systemic disease can cause primary testis dysfunction in addition to suppressing gonadotropin production. In cirrhosis, a combined testicular and pituitary abnormality leads to decreased testosterone production independent of the direct toxic effects of ethanol. The testes are sensitive to radiation damage. Doses >200 mGy (20 rad) are associated with increased follicle-stimulating hormone and luteinizing hormone levels and damage to the spermatogonia. After ~800 mGy (80 rad), oligospermia or azoospermia develops, and higher doses may obliterate the germinal epithelium. Permanent androgen deficiency in adult men is uncommon after therapeutic radiation; however, most boys given direct testicular radiation therapy for acute lymphoblastic leukemia have permanently low testosterone levels. Sperm banking should be considered before patients undergo radiation treatment or chemotherapy.

IX-41. The answer is D. *(Chap. 384)* Gynecomastia is a relatively common complaint in men and may be caused by either obesity with adipose tissue expansion in the breast or by an increased estrogen-to-androgen ratio in which there is true glandular enlargement, as in this case. If the breast is unilaterally enlarged or if it is hard or fixed to underlying tissue, mammography is indicated. Alternatively, if cirrhosis or a causative drug is present, these may be adequate explanations, particularly when gynecomastia develops later in life in previously fertile men. If the breast tissue is >4 cm or there is evidence of very small testes and no causative drugs or liver disease, a search for alterations in serum testosterone, luteinizing hormone, follicle-stimulating hormone, estradiol, and human chorionic gonadotropin (hCG levels) should be undertaken. An androgen deficiency or resistance syndrome may be present, or an hCG secreting tumor may be found. In this case, spironolactone is the likely culprit, and it may be stopped or switched to eplerenone and gynecomastia reassessed.

IX-42. The answer is D. *(Chap. 385)* For the majority of the ovulatory cycle, the reproductive system functions in a classic endocrine negative feedback mode. Estradiol and progesterone inhibit gonadotropin-releasing hormone (GnRH) secretion, acting through kisspeptin and dynorphin in the KNDy neurons, and the inhibins act at the pituitary to selectively

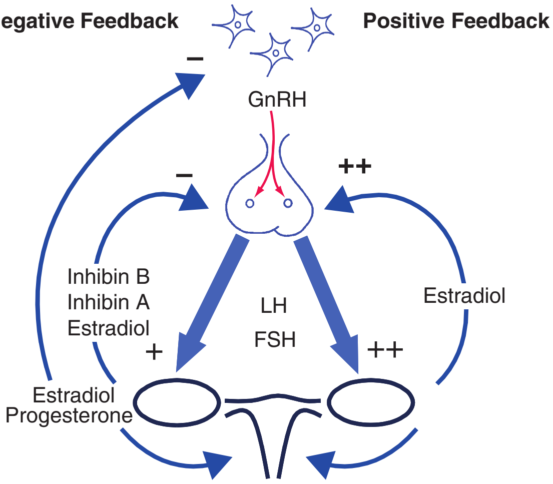


FIGURE IX-42 FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone.

inhibit follicle-stimulating hormone (FSH) synthesis and secretion (Figure IX-42). Estradiol also contributes to negative feedback at the pituitary with an effect that is greater for FSH than luteinizing hormone (LH). This tightly regulated negative feedback control of FSH is critical for development of the single mature oocyte that characterizes normal reproductive function in women. In addition to these negative feedback controls, the menstrual cycle is uniquely dependent on estrogen-induced positive feedback to produce an LH surge that is essential for ovulation of a mature follicle. Estrogen negative feedback in women occurs primarily at the hypothalamus with a small pituitary contribution, whereas estrogen positive feedback occurs at the pituitary in women with upregulation of GnRH signaling. In women, hypothalamic GnRH secretion plays a permissive role in generating the preovulatory gonadotropin surge, a mechanism that differs significantly from that in rodents and other species that rely on seasonal and circadian cues, in which a surge of GnRH also occurs.

IX-43. **The answer is B.** *(Chap. 385)* The first menstrual period (menarche) occurs relatively late in the series of developmental milestones that characterize normal pubertal development in girls. Menarche is preceded by the appearance of pubic and then axillary hair (adrenarche) as a result of maturation of the zona reticularis in the adrenal gland and increased adrenal androgen secretion, particularly dehydroepiandrosterone. The triggers for adrenarche remain unknown but may involve increases in body mass index, as well as in utero and neonatal factors. Menarche is also preceded by breast development (thelarche). The breast is exquisitely sensitive to the very low levels of estrogen that result from peripheral conversion of adrenal androgens and the low levels of estrogen secreted from the ovary early in pubertal maturation. Breast development precedes the appearance of pubic and axillary hair in approximately 60% of girls. The interval between the onset of breast development and menarche is approximately 2 years. There has been a gradual decline in the age of menarche over the past century, attributed in large part to improvements in nutrition, and there is a relationship between adiposity and earlier sexual maturation in girls.

IX-44. **The answer is E.** *(Chap. 386)* Pelvic inflammatory disease (PID) most commonly presents with bilateral lower abdominal pain. It is generally of recent onset and is exacerbated by intercourse or jarring movements. Fever is present in about half of these patients; abnormal uterine bleeding occurs in about one-third. New vaginal discharge, urethritis, and chills may be present, but they are less specific signs. With public health efforts to control sexually transmitted diseases, the rate and severity of PID have declined in the United States and Europe; however, this is not the case in the developing world. Subclinical PID with its attendant risks of infertility and ectopic pregnancy remains a significant problem worldwide. Public health and professional organizations recommend annual testing for *Chlamydia trachomatis* in all sexually active women <25 and both *C. trachomatis* and *Neisseriae gonorrhea* in all women at increased risk. Ectopic pregnancy is associated with right- or left-sided lower abdominal pain, with clinical signs generally appearing 6–8 weeks after the last normal menstrual period. In this case, the pregnancy test is negative and she has had a recent menstrual period. Vaginal bleeding occurs in ~50% of cases. Orthostatic signs and fever may be present. Risk factors include the presence of known tubal disease, previous ectopic pregnancies, a history of infertility, diethylstilbestrol exposure of the mother in utero, or a history of pelvic infections. Rupture of the fallopian tube remains a life-threatening emergency; the incidence depends on access to care but is ~18% in developed countries. Endometriosis is a cause of chronic and cyclic pelvic pain. It results from the presence of endometrial glands and stroma outside the uterus. These deposits of ectopic endometrium respond to hormonal stimulation and cause dysmenorrhea, which begins several days before menses. Endometriosis also may be associated with painful intercourse, painful bowel movements, and tender nodules in the uterosacral ligament. Appendicitis is a cause of acute abdominal pain, but the examination, history, and vaginal discharge support PID.

IX-45. **The answer is B.** *(Chap. 386)* The first step in the evaluation of amenorrhea is assessment of the uterus and outflow tract. If normal, subsequent evaluation should include ruling out pregnancy followed by measurement of androgens (testosterone and dehydroepiandrosterone sulfate), follicle-stimulating hormone (FSH), and prolactin. As shown in Figure IX-45, this patient has findings consistent with a neuroendocrine tumor and should receive an MRI. Androgen resistance syndrome requires gonadectomy because there is risk of gonadoblastoma in the dysgenetic gonads. Whether this should be performed in early childhood or after completion of breast development is controversial.

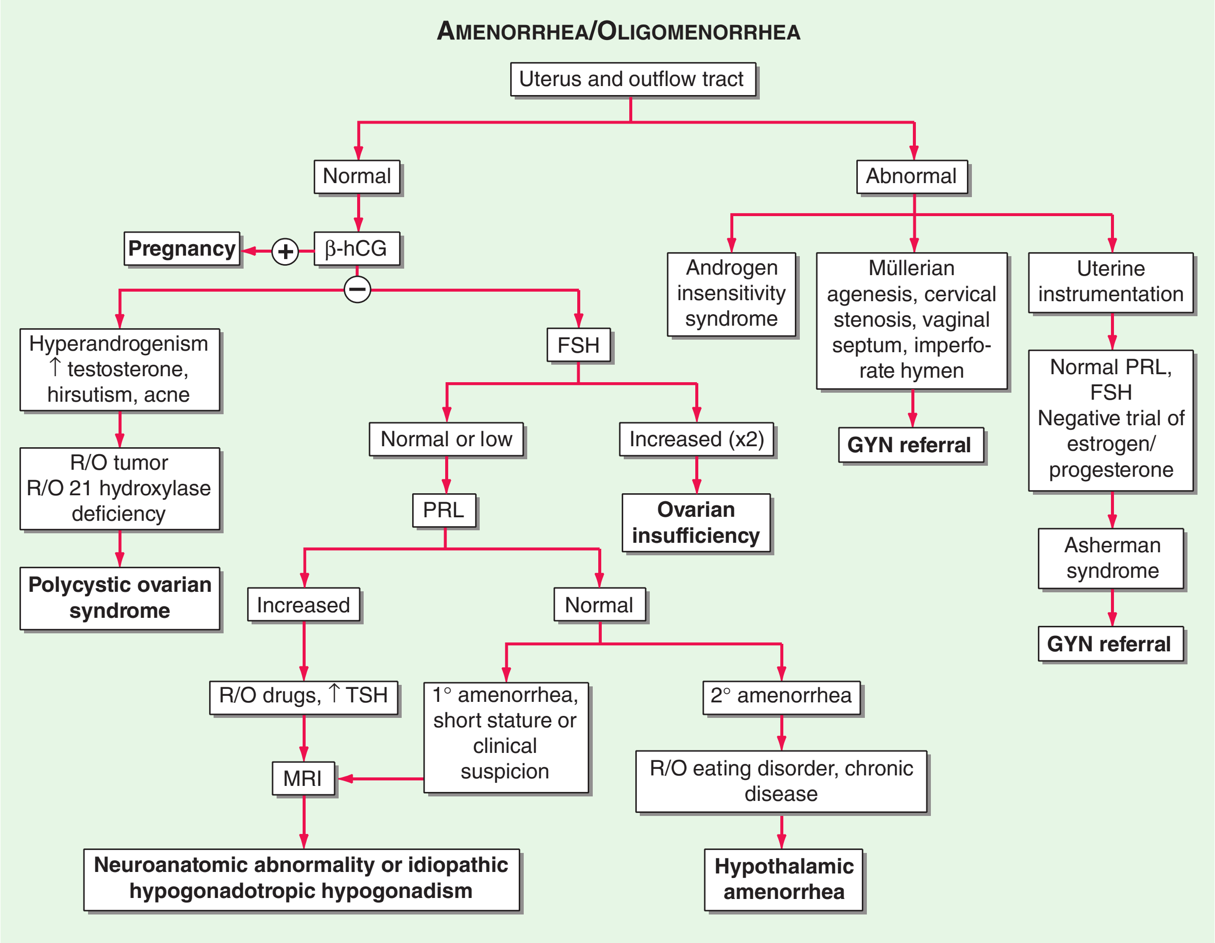

AMENORRHEA/OLIGOMENORRHEA
Uterus and outflow tract
Normal
Abnormal
Pregnancy
+
β-hCG
−
Androgen insensitivity syndrome
Müllerian agenesis, cervical stenosis, vaginal septum, imperforate hymen
Uterine instrumentation
Hyperandrogenism ↑ testosterone, hirsutism, acne
FSH
Normal PRL, FSH Negative trial of estrogen/ progesterone
Normal or low
Increased (x2)
GYN referral
R/O tumor R/O 21 hydroxylase deficiency
PRL
Ovarian insufficiency
Asherman syndrome
Polycystic ovarian syndrome
Increased
Normal
GYN referral
R/O drugs, ↑ TSH
1° amenorrhea, short stature or clinical suspicion
2° amenorrhea
MRI
R/O eating disorder, chronic disease
Neuroanatomic abnormality or idiopathic hypogonadotropic hypogonadism
Hypothalamic amenorrhea

FIGURE IX-45 Algorithm for evaluation of amenorrhea. *Abbreviations:* β-hCG, β-human chorionic gonadotropin; FSH, follicle-stimulating hormone; GYN, gynecologist; MRI, magnetic resonance imaging; PRL, prolactin; R/O, rule out; TSH, thyroid-stimulating hormone.

IX-46. The answer is D. *(Chap. 386)* Polycystic ovarian syndrome (PCOS) is diagnosed based on a combination of clinical or biochemical evidence of hyperandrogenism, amenorrhea or oligomenorrhea, and the ultrasound appearance of polycystic ovaries. Approximately half of patients with PCOS are obese, and abnormalities in insulin dynamics are common, as is metabolic syndrome. Symptoms generally begin shortly after menarche and are slowly progressive. Patients may develop dysfunctional uterine bleeding as defined by frequent or heavy uterine bleeding. A major abnormality in patients with PCOS is the failure of regular predictable ovulation. Thus, these patients are at risk for the development of dysfunctional bleeding and endometrial hyperplasia associated with unopposed estrogen exposure. Endometrial protection can be achieved with the use of oral contraceptives or progestins (medroxyprogesterone acetate, 5–10 mg, or Prometrium, 200 mg daily for 10–14 days of each month). Oral contraceptives are also useful for management of hyperandrogenic symptoms, as is spironolactone, which functions as a weak androgen receptor blocker. Clomiphene and letrozole are used in PCOS patients who are interested in fertility. Corticosteroids will worsen this patient's obesity and hyperglycemia. Testosterone will worsen the PCOS because the disorder is driven by androgen excess.

IX-47. The answer is E. *(Chap. 387)* Hirsutism is most often idiopathic or the consequence of androgen excess associated with polycystic ovary syndrome (Table IX-47). Less frequently,

TABLE IX-47 Causes of Hirsutism

- Gonadal hyperandrogenism
    - Ovarian hyperandrogenism
    - Polycystic ovary syndrome/functional ovarian hyperandrogenism
    - Ovarian steroidogenic blocks
    - Syndromes of extreme insulin resistance
    - Ovarian neoplasms
    - Hyperthecosis
- Adrenal hyperandrogenism
    - Premature adrenarche
    - Functional adrenal hyperandrogenism
    - Congenital adrenal hyperplasia (nonclassic and classic)
    - Abnormal cortisol action/metabolism
    - Adrenal neoplasms
- Other endocrine disorders
    - Cushing syndrome
    - Hyperprolactinemia
    - Acromegaly
- Peripheral androgen overproduction
    - Obesity
    - Idiopathic
- Pregnancy-related hyperandrogenism
    - Hyperreactio luteinalis
    - Thecoma of pregnancy
- Drugs
    - Androgens
    - Oral contraceptives containing androgenic progestins
    - Minoxidil
    - Phenytoin
    - Diazoxide
    - Cyclosporine
    - Valproic Acid
- True hermaphroditism

it may result from adrenal androgen overproduction as occurs in nonclassic congenital adrenal hyperplasia. Rarely, it is a harbinger of a serious underlying condition. Cutaneous manifestations commonly associated with hirsutism include acne and male-pattern balding (androgenic alopecia). *Virilization* refers to a condition in which androgen levels are sufficiently high to cause additional signs and symptoms, such as deepening of the voice, breast atrophy, increased muscle bulk, clitoromegaly, and increased libido. Virilization may be due to benign hyperplasia of ovarian theca and stroma cells (e.g., *hyperthecosis)*; it may also result from an ovarian or adrenal neoplasm. A variety of endocrine conditions can lead to hirsutism including hyperprolactinemia. Excess cortisol rather than the cortisol deficiency seen in Addison disease can cause hirsutism. Hypothyroidism, growth hormone deficiency, and menopause are not known to cause hirsutism.

IX-48. **The answer is D.** *(Chap. 387)* Hirsutism, which is defined as androgen-dependent excessive male pattern hair growth, affects approximately 10% of women. Hirsutism is most often idiopathic or the consequence of androgen excess associated with the polycystic ovarian syndrome. Less frequently, it may result from adrenal androgen overproduction as occurs in nonclassic congenital adrenal hyperplasia. Historic elements relevant to the assessment of hirsutism include the age at onset and rate of progression of hair growth and associated symptoms or signs (e.g., acne). Depending on the cause, excess hair growth typically is first noted during the second and third decades of life. The growth is usually slow but progressive. Sudden development and rapid progression of hirsutism suggest the possibility of an androgen-secreting neoplasm, in which case virilization also may be present. Physical examination should include measurement of height and weight and calculation of body mass index (BMI). A BMI >30 kg/m^2 is often seen in association with hirsutism, probably the result of increased conversion of androgen precursors to testosterone.

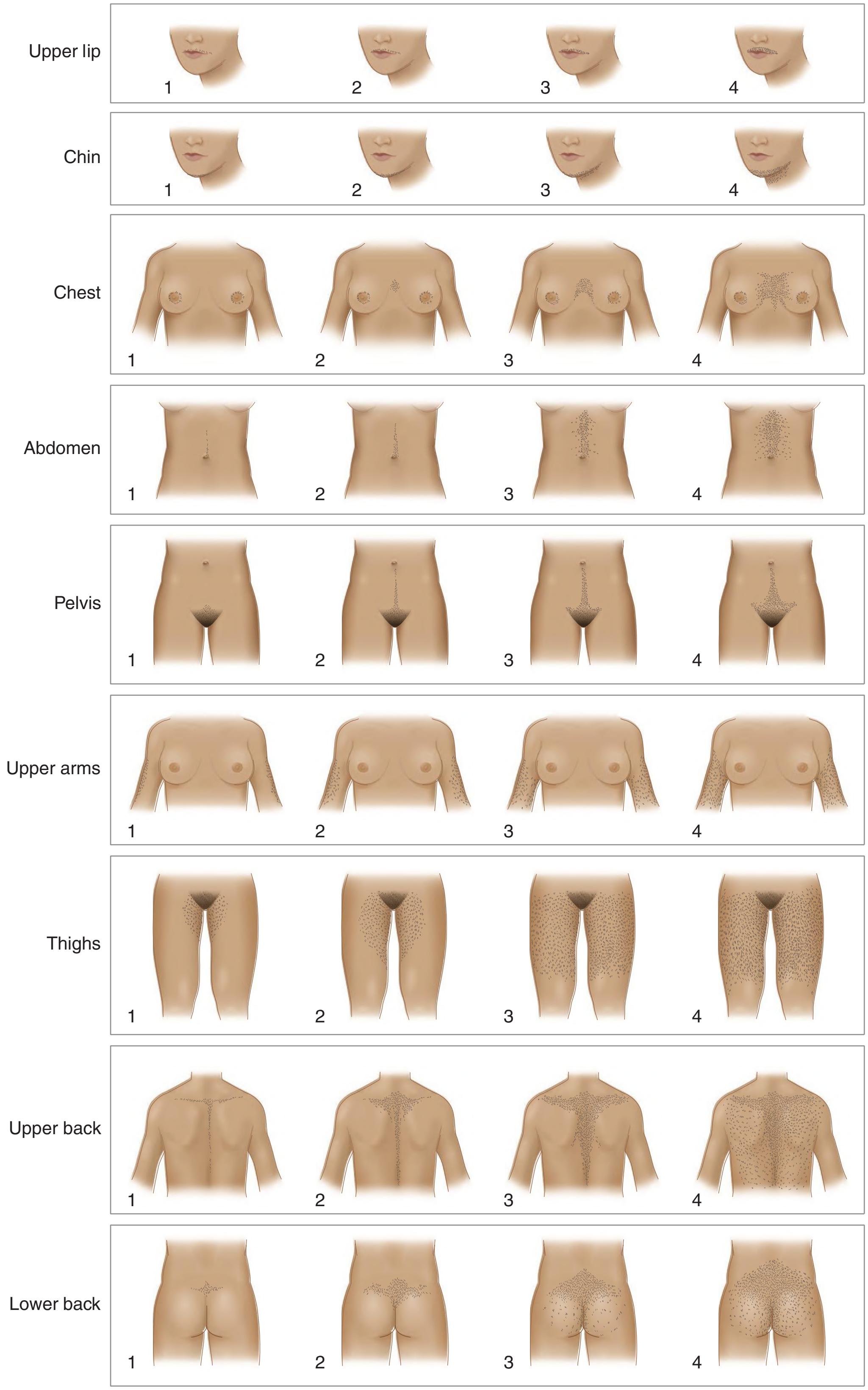

Upper lip
Chin
Chest
Abdomen
Pelvis
Upper arms
Thighs
Upper back
Lower back
1
2
3
4

FIGURE IX-48 Modified with permission from DeGroot LJ et al: *Endocrinology*, 5th ed. Philadelphia: Saunders, 2006.

Notation should be made of blood pressure, because adrenal causes may be associated with hypertension. Cutaneous signs sometimes associated with androgen excess and insulin resistance include acanthosis nigricans and skin tags. An objective clinical assessment of hair distribution and quantity is central to the evaluation in any woman presenting with hirsutism. This assessment permits the distinction between hirsutism and hypertrichosis and provides a baseline reference point to gauge the response to treatment. A simple and commonly used method to grade hair growth is the modified scale of Ferriman and Gallwey, in which each of nine androgen-sensitive sites is graded from 0 to 4 (Figure IX-48). Approximately 95% of white women have a score below 8 on this scale; thus, it is normal for most women to have some hair growth in androgen-sensitive sites. Scores above 8 suggest excess androgen-mediated hair growth, a finding that should be assessed further by means of hormonal evaluation. In racial/ethnic groups that are less likely to manifest hirsutism (e.g., Asian women), additional cutaneous evidence of androgen excess should be sought, including pustular acne and thinning scalp hair.

IX-49. **The answer is C.** *(Chap. 388)* Ovarian mass and fertility decline sharply after age 35 and even more precipitously during perimenopause; depletion of primary follicles, a process that begins before birth, occurs steadily until menopause. In perimenopause, intermenstrual intervals shorten significantly (typically by 3 days) as a result of an accelerated follicular phase. Follicle-stimulating hormone (FSH) levels rise because of altered folliculogenesis and reduced inhibin secretion. In contrast to the consistently high FSH and low estradiol levels seen in menopause, perimenopause is characterized by "irregularly irregular" hormone levels. The propensity for anovulatory cycles can produce a hyperestrogenic, hypoprogestagenic environment that may account for the increased incidence of endometrial hyperplasia or carcinoma, uterine polyps, and leiomyoma observed among women of perimenopausal age. Mean serum levels of selected ovarian and pituitary hormones during the menopausal transition are shown in Figure IX-49. With transition into menopause, estradiol levels fall markedly, whereas estrone levels are relatively preserved, a pattern reflecting peripheral aromatization of adrenal and ovarian androgens. Levels of FSH increase more than those of luteinizing hormone, presumably because of the loss of inhibin as well as estrogen feedback.

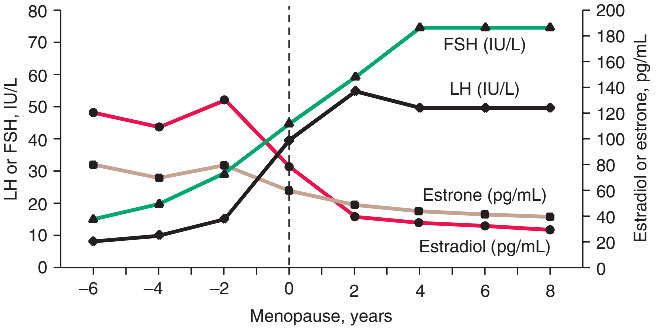


FIGURE IX-49 *Abbreviations:* FSH, follicle-stimulating hormone; LH, luteinizing hormone. (Adapted with permssion from Rannevik G et al: A longitudinal study of the perimenopausal transition: altered profiles of steroid and pituitary hormones, SHBG and bone mineral density. *Maturitas* 21:103, 1995.)

IX-50. **The answer is E.** *(Chap. 388)* The Women's Health Initiative was the largest study of hormone therapy to date, including 27,000 post-menopausal women age 50 to 79 years who were followed for an average of 5–7 years. It was presumed that hormone replacement in this group of women would decrease cardiovascular risk. However, the trial was stopped early because of an unfavorable risk-benefit ratio in the estrogen-progestin arm and an increased risk of stroke that was not offset by lower coronary heart disease in the estrogen-only arm. Endometrial cancer risk was higher in patients with an intact uterus who were taking estrogen only. Use of progesterone eliminated this risk. Unopposed estrogen was associated with an increased risk of stroke that far outweighed the decreased risk of coronary heart disease. Estrogen-progestin together was associated with an increased risk of coronary heart disease. Osteoporosis risk was decreased in both the estrogen and estrogen-progestin groups. Venous thromboembolism risk was higher in both treatment groups as well. These therapies do reduce important menopausal symptoms such as hot flashes and vaginal drying. This seminal study caused a dramatic reevaluation of the use of estrogen and progesterone in post-menopausal women to reduce cardiovascular risk. In addition, it reiterated the importance of well-designed clinical studies to test accepted dogma.

IX-51. **The answer is C.** *(Chap. 389)* Although recent statistics indicate a decrease in unintended pregnancy in the United States, 45% of births are still the result of unintended pregnancy; approximately one-third of these result from incorrect use or failure of contraceptives, and >50% result in induced abortion. The effectiveness of a given method of contraception does not just depend on the efficacy of the method itself. Discrepancies between theoretical and actual effectiveness emphasize the importance of patient education and adherence when considering various forms of contraception (Table IX-58). Progestin-containing Intrauterine devices have a >99% theoretical and actual effectiveness. Contraceptive use is stratified by race/ethnicity with higher oral contraceptive use in white women and greater use of long-acting reversible contraceptive (LARC) methods in Latina women. For oral contraceptives, discontinuation rates are highest among Black women whereas there is no racial/ethnic differences for LARC methods. Knowledge of the advantages and disadvantages of each contraceptive is essential for counseling an individual about the methods that are safest and most consistent with his or her lifestyle.

TABLE IX-51 Effectiveness of Different Forms of Contraception

Method of Contraception	Theoretical Effectiveness (%)	Actual Effectiveness (%)	Continued Use at 1 Year (%)	Use of Method by U.S. Women at Risk of Unintended Pregnancy (%)
No Method	15	15		10
Fertility awareness	96	76	47	1.2
Withdrawal	96	78	46	4.4
Barrier methods				
Condoms	98	82	43	13.7
Diaphragm	94	82	57	2
Spermicides	82	72	43	1
Sterilization				
Female	99.5	99.5	100	22.6
Male	99.5	99.9	100	7.4
Intrauterine device				9.3
Copper T	99.4	99.8	85	
Progestin-containing	99.8	99.8	88	
Hormonal contraceptives				
Combined and progestin only	99.7	91	67	23.3
Transdermal patch	99.7	91	67	0.5
Vaginal ring	99.7	91	67	1.8
Implant				1.2
Depo-Provera	99.8	94	56	
Nexplanon	99.5	99.5	84	
Emergency contraception				0.3

Source: Data from Trussell J et al: *Contraceptive Efficacy, in Contraceptive Technology*, 20th revised ed, Hatcher RA et al (eds). New York: Ardent Media, 2011; CDC. NCHS National Survey of Family Growth, 2011-2013; Jones J, Mosher WD, Daniels K: Current contraceptive use in the United States, 2006-2010, and changes in patterns of use since 1995, National Health Statistics Reports, 2012, No. 60, http://www.cdc.gov/nchs/data/nhsr/nhsr060.pdf; and Birgisson NE et al: Preventing unintended pregnancy: the contraceptive CHOICE project in review. *J Womens Health (Larchmt)* 24:349, 2015.

IX-52. The answer is A. *(Chap. 389)* Because of their ease of use and efficacy, oral contraceptive pills are the most widely used form of hormonal contraception. They act by suppressing ovulation, changing cervical mucus, and altering the endometrium. The current formulations are made from synthetic estrogens and progestins. At the currently used doses, patients must be cautioned not to miss pills due to the potential for ovulation and this may be particularly important in obese women. Side effects, including breakthrough bleeding, amenorrhea, breast tenderness, and weight gain, often respond to a change in formulation. Oral contraceptive use is associated with a decreased risk of endometrial, ovarian, and colon cancer. However, even the lower dose oral contraceptives have been associated with an increased risk of breast cancer and cardiovascular disease (myocardial infarction, stroke, venous thromboembolism [VTE]), but the absolute excess risk is extremely low. VTE risk is higher with the third-generation than the second-generation progestins, and the risk of stroke and VTE is also higher with drospirenone (although not cyproterone). Again, the absolute excess risk is small for most patients. In this patient, the combination of her age and smoking more than 15 cigarettes a day is an absolute contraindication for hormonal oral contraceptive pills (Table IX-52). Well-controlled hypertension is a relative contraindication.

TABLE IX-52 Oral Contraceptives: Contraindications and Disease Risk

Contraindications
Absolute
Women age >35 years who smoke ≥15 cigarettes per day
Known ischemic heart disease or multiple risk factors for cardiovascular disease (older age, smoking, diabetes, and hypertension)
Previous thromboembolic event, stroke, or known thrombogenic mutations
Complicated valvular heart disease
Complicated solid organ transplantation
Hypertension (systolic ≥160 mmHg or diastolic ≥100 mmHg)
Systemic lupus erythematous (positive or unknown antiphospholipid antibodies
Cirrhosis, hepatic adenoma or hepatoma
Pregnancy and early postpartum (<21 days)
Undiagnosed abnormal uterine bleeding
Relative
Hypertension (adequately controlled or systolic 140–159 or diastolic 90–99)
Women receiving anticonvulsant drug therapy
Women following bariatric surgery (malabsorptive procedure)
Disease Risks
Increased
Coronary heart disease—increased in smokers >35; no relation to progestin type
Hypertension—relative risk 1.8 (current users) and 1.2 (previous users)
Venous thrombosis—relative risk ~4; may be higher with third-generation progestin, drospirenone, and patch; compounded by obesity (10-fold increased risk compared with nonobese, no OCP); markedly increased with factor V Leiden or prothrombin gene mutations
Stroke—slight increase; unclear relation to migraine headache
Cerebral vein thrombosis—relative risk ~13–15; synergistic with prothrombin gene mutation
Cervical cancer—relative risk 2–4
Breast cancer—may increase risk, particularly in carriers of *BRCA1* and possibly *BRCA2*
Decreased
Ovarian cancer—50% reduction in risk
Endometrial cancer—40% reduction in risk

Abbreviation: OCP, oral contraceptive pill.

IX-53. The answer is C. *(Chap. 389)* Infertility, defined as the inability to conceive after 12 months of unprotected intercourse, is a common problem in the United States, with an estimated 15% of couples affected. Initial evaluation should include an evaluation of current menstrual history, counseling regarding the appropriate timing of intercourse, and education regarding modifiable risk factors such as drug use, alcohol intake, smoking, caffeine, and obesity. Male factors are at the root of approximately 25% of cases of infertility, unexplained infertility is found in 17% of cases, and female causes underlie 58% of infertility cases. Among the female causes, the most common is amenorrhea/ovulatory dysfunction, which is present in 46% of cases. This is most frequently due to hypothalamic or pituitary causes, or polycystic ovary syndrome. Tubal defects and endometriosis are less common.

IX-54. The answer is C. *(Chap. 389)* Evaluation of infertility should include evaluation of common male and female factors that could be contributing. Abnormalities of menstrual function are the most common cause of female infertility, and initial evaluation of infertility should include evaluation of ovulation and assessment of tubal and uterine patency. The female partner reports an episode of gonococcal infection with symptoms of pelvic inflammatory disease, which would increase her risk of infertility due to tubal scarring and occlusion. A hysterosalpingogram is indicated. If there is evidence of tubal abnormalities, many experts recommend in vitro fertilization for conception because these women are at increased risk of ectopic pregnancy if conception occurs. The female partner reports some irregularity of her menses, suggesting anovulatory cycles, and thus, evidence of ovulation should be determined by assessing hormonal levels. There is no evidence that prolonged use of oral contraceptives affects fertility adversely. Angiotensin-converting enzyme inhibitors, including lisinopril, are known teratogens when taken by women but have no effect on chromosomal abnormalities in men. Recent marijuana use may be associated with increased risk of infertility, and in vitro studies of human sperm exposed to a cannabinoid derivative showed decreased motility. However, no studies have shown long-term decreased fertility in men who previously used marijuana.

IX-55. The answer is C. *(Chap. 390)* Medication-induced erectile dysfunction (ED) is estimated to occur in 25% of men seen in general medical outpatient clinics (Table IX-55). The adverse effects related to drug therapy are additive, especially in older men. In addition to the drug itself, the underlying disease being treated is likely to contribute to sexual dysfunction. Among the antihypertensive agents, the thiazide diuretics and beta blockers have been implicated most frequently. Calcium channel blockers and angiotensin converting-enzyme inhibitors are cited less frequently. These drugs may act directly at the corporal level (e.g., calcium channel blockers) or indirectly by reducing pelvic blood pressure, which is important in the development of penile rigidity. α-Adrenergic blockers are less likely to cause ED. Estrogens, gonadotropin-releasing hormone agonists, H_2 antagonists, and spironolactone cause ED by suppressing gonadotropin production or by blocking androgen action. Antidepressant and antipsychotic agents—particularly neuroleptics, tricyclics, and selective serotonin reuptake inhibitor (SSRIs)—are associated with erectile, ejaculatory, orgasmic, and sexual desire difficulties. Among the SSRIs, paroxetine and escitalopram have been associated with the highest risk of sexual dysfunction. Bupropion, nefazodone, and mirtazapine appear less likely to cause sexual dysfunction. A number of molecular pathways have been implicated in antidepressant-induced sexual adverse events. Serotonin has been hypothesized to inhibit normal sexual response by decreasing dopamine-enhanced libido, arousal, and erection, and by increasing prolactin release. SSRIs have also been shown to be potent inhibitors of nitric oxide synthesis. ED occurs in 35–75% of men with diabetes mellitus. Pathologic mechanisms are related primarily to diabetes-associated vascular and neurologic complications. Diabetic macrovascular complications are related mainly to age, whereas microvascular complications correlate with the duration of diabetes and the degree of glycemic control. Metformin is not associated with ED.

TABLE IX-55 Drugs Associated with Erectile Dysfunction

Classification	Drugs
Diuretics	Thiazides
	Spironolactone
Antihypertensives	Calcium channel blockers
	Methyldopa
	Clonidine
	Reserpine
	Beta blockers
	Guanethidine
Cardiac/antihyperlipidemics	Digoxin
	Gemfibrozil
	Clofibrate
Antidepressants	Selective serotonin reuptake inhibitors
	Tricyclic antidepressants
	Lithium
	Monoamine oxidase inhibitors
Tranquilizers	Butyrophenones
	Phenothiazines
H_2 antagonists	Ranitidine
	Cimetidine
Hormones	Progesterone
	Estrogens
	Corticosteroids
	GnRH agonists
	5α-Reductase inhibitors
	Cyproterone acetate
Cytotoxic agents	Cyclophosphamide
	Methotrexate
	Roferon-A
Anticholinergics	Disopyramide
	Anticonvulsants
Recreational	Ethanol
	Cocaine
	Marijuana

Abbreviation: GnRH, gonadotropin-releasing hormone.

IX-56. The answer is D. *(Chap. 390)* The phosphodiesterase-5 inhibitors, including sildenafil, tadalafil, vardenafil, and avanafil, are the only approved and effective oral agents for the treatment of erectile dysfunction (ED). They are effective for the treatment of a broad range of causes, including psychogenic, diabetic, vasculogenic, post–radical prostatectomy (nerve-sparing procedures), and spinal cord injury. Androgen therapy with testosterone may be effective to improve libido and erectile function in patients with low serum testosterone, but this patient has a normal serum testosterone for age. 5α-Reductase inhibitors, such as finasteride, are used to treat prostatic hypertrophy and act as antiandrogens; thus, they may cause ED. Corticosteroids and selective serotonin reuptake inhibitor medications are associated with causing ED.

IX-57. The answer is B. *(Chap. 390)* In post-menopausal women, estrogen replacement therapy may be helpful in treating vaginal atrophy, decreasing coital pain, and improving clitoral sensitivity. Estrogen replacement in the form of local cream is the preferred method, as it avoids systemic side effects. There is no proven efficacy of phosphodiesterase-5 inhibitors, such as sildenafil, in female sexual dysfunction despite similar sexual response physiology in women as men. Selective serotonin reuptake inhibitors used for depression, such as paroxetine, may cause sexual dysfunction in women. Tamoxifen and anastrozole are antiestrogens used to treat breast cancer and may cause vaginal atrophy and female sexual dysfunction.

IX-58. **The answer is A.** *(Chap. 391)* The leading causes of death are the same in women and men: (1) heart disease and (2) cancer (Figure IX-58). The leading cause of cancer death, lung cancer, is the same in both sexes. Breast cancer is the second leading cause of cancer death in women, but it causes about 60% fewer deaths than does lung cancer. Men are more likely than women to die from suicide and accidents. For example, accidents are the third leading cause of death in men but the sixth leading cause of death in women. Stroke, chronic lower respiratory disease, and Alzheimer's disease cause a larger percentage of deaths in women than in men. Suicide is among the 10 leading causes of death in men but not in women.

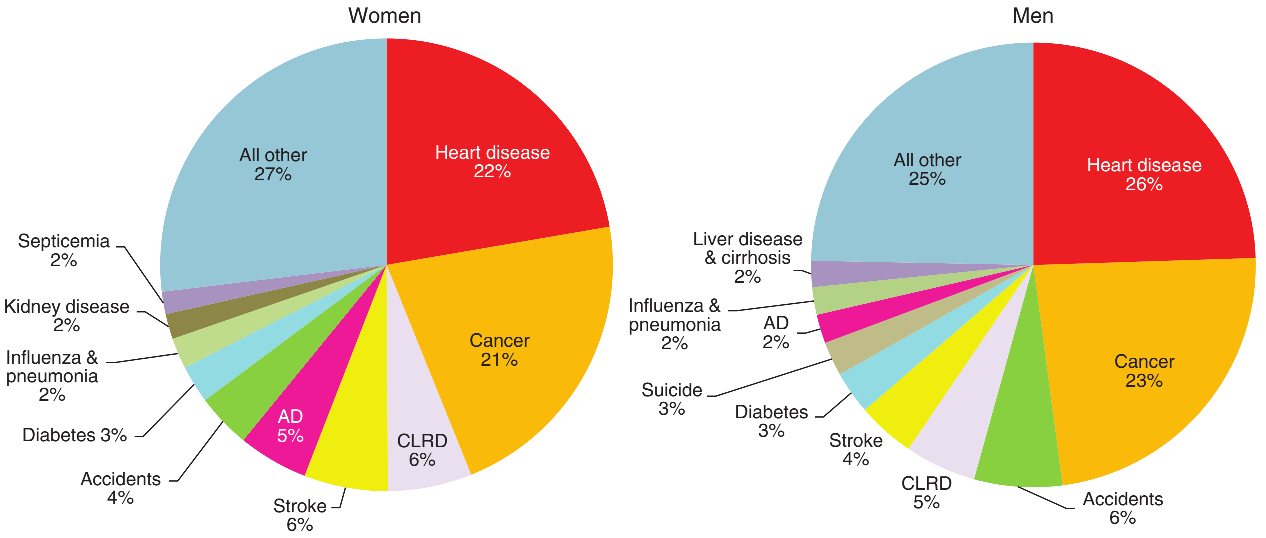


FIGURE IX-58 *Abbreviations:* AD, Alzheimer's disease; CLRD, chronic lower respiratory disease. (Data from Kochanek KD et al: Deaths: final data for 2014. *Natl Vital Stat Rep* 65:1, 2016.)

IX-59. **The answer is E.** *(Chap. 391)* Women are more sensitive to insulin than are men. Despite this, the prevalence of type 2 diabetes mellitus (DM) is similar in men and women. There is a sex difference in the relationship between endogenous androgen levels and DM risk. Higher bioavailable testosterone levels are associated with increased risk in women, whereas lower bioavailable testosterone levels are associated with increased risk in men. Polycystic ovary syndrome, preeclampsia, pregnancy-associated hypertension, and gestational DM—common conditions in pre-menopausal women—are associated with a significantly increased risk for type 2 DM. Among individuals with DM, women have a greater risk for myocardial infarction than do men. Women with DM have a sixfold greater risk of dying of cerebrovascular disease (CVD) compared with women without DM. Pre-menopausal women with DM lose the cardioprotective effect of female sex and have rates of CVD identical to those in males. These women have impaired endothelial function and reduced coronary vasodilatory responses, which may predispose to cardiovascular complications. Women with DM are more likely to have left ventricular hypertrophy. Women with DM receive less aggressive treatment for modifiable CVD risk factors than men with DM.

IX-60. **The answer is C.** *(Chap. 391)* Coronary heart disease (CHD) is the most common cause of death in men and women, but important sex differences exist in the presentation and treatment of CHD. At the time of presentation of CHD, women are typically about 10–15 years older than men with CHD. In addition, women have a greater number of medical comorbidities at the time of diagnosis, including hypertension, heart failure, and diabetes mellitus. Angina is the most common presenting symptom of CHD in women and may have atypical features including nausea, indigestion, and upper back pain. Women who present with a myocardial infarction (MI) more often present with cardiogenic shock or cardiac arrest, whereas men have a greater risk of ventricular tachycardia on presentation with MI. In the past, women had a greater risk of death due to MI when presenting at younger ages, but this gap has decreased in recent years. However, women are still referred less often by physicians for diagnostic and therapeutic cardiovascular procedures, and there are more false-positive and false-negative diagnostic tests in women. Women are also less likely than men to receive angioplasty, thrombolysis, coronary artery bypass grafting, aspirin, and beta blockers. Despite this, the 5- and 10-year survival rates following coronary artery bypass grafting are the same between the sexes.

IX-61. **The answer is E.** *(Chap. 391)* Women do have a longer and more vulnerable QT interval on average. Two-thirds of cases of drug-induced torsades de pointes, a rare, life-threatening ventricular arrhythmia, occur in women. Testosterone administered to women or men increases the incidence or severity of obstructive sleep apnea. Women are more sensitive to insulin than men. Despite this, the prevalence of type 2 diabetes is similar in men and women. There is a sex difference in the relationship between endogenous androgen levels and diabetes risk. Higher bioavailable testosterone levels are associated with increased risk in women, whereas lower bioavailable testosterone levels are associated with increased risk in men. Obesity has been shown to increase the risk for endometrial cancer in women. This is likely due to the increased extragonadal source of estrogen produced by adipose tissue. Although most autoimmune diseases are more common in women (with type 1 diabetes and ankylosing spondylitis as exceptions), the use of oral contraceptives and hormone therapy in women does not increase the risk of autoimmune diseases.

IX-62. **The answer is B.** *(Chap. 392)* In epidemiologic surveys, low total and bioavailable testosterone concentrations have been associated with decreased appendicular skeletal muscle mass and strength, decreased self-reported physical function, higher visceral fat mass, insulin resistance, and increased risk of coronary artery disease and mortality (Table IX-62). An analysis of signs and symptoms in older men in the European Male Ageing Study revealed a syndromic association of sexual symptoms with total testosterone levels <320 ng/dL and free testosterone levels <64 pg/mL in community-dwelling older men. Low testosterone levels have not been associated with dementia, erectile dysfunction, or major depression.

TABLE IX-62 Association of Testosterone Levels with Outcomes in Older Men

1. Positively associated with:
    - Muscle mass and muscle strength
    - Physical function
    - Sexual desire
    - Bone mineral density, bone geometry, and volumetric bone mineral density
2. Negatively associated with:
    - Coronary artery disease
    - Visceral fat
    - Diabetes mellitus
    - Metabolic syndrome
    - Mortality
    - Falls and fracture risk
    - Frailty
3. Not associated with:
    - Lower urinary tract symptoms
    - Erectile dysfunction
    - Dementia
    - Major depression

IX-63. **The answer is E.** *(Chap. 392)* The patient has lower urinary tract symptoms (LUTS) presumably from benign prostatic hyperplasia. Several simple steps such as reducing caffeine and alcohol intake, especially late in the day, taking the diuretic medication early in the day, avoiding excessive water intake close to bedtime, double voiding to ensure complete emptying of the bladder may be helpful in reducing the severity of symptoms. Men with mild to moderate bothersome LUTS can be treated effectively using α-adrenergic antagonists, steroid 5α-reductase inhibitors, PDE5 inhibitors, or anticholinergic agents alone or in combination. Selective α-adrenergic antagonists are typically the first line of therapy; their side effects may include hypotension, dizziness, nasal congestion, headache, and floppy iris syndrome. In men with probable benign prostate obstruction with gland enlargement and LUTS, therapy with steroid 5α-reductase inhibitors, finasteride, or dutasteride, for one or more years improves urinary symptoms and flow rate and reduces prostatic volume. Long-term treatment with 5α-reductase inhibitors can reduce the risk of acute urinary retention and need for prostate surgery. Combined administration of steroid 5α-reductase inhibitor and α(1)-adrenergic blocker can rapidly improve urinary symptoms and reduce the relative risk of acute urinary retention and surgery. PDE5 inhibitors when administered chronically alone or in combination with α-adrenergic blockers are effective in improving LUTS and erectile dysfunction through their effects on nitric oxide—cyclic guanosine monophosphate in the bladder, urethra, and prostate. PDE5 inhibitors do not improve uroflow parameters, and their hypotensive effect may be potentiated by α(1)-adrenergic blockers. Anticholinergic drugs are used for the treatment of overactive bladder in men with prominent urgency symptoms and no evidence of elevated postvoid residual urine. Containment products, such as pads, can help improve social life in men who have severe storage symptoms, including incontinence. Surgery is indicated when medical therapy fails, symptoms progress in spite of medical therapy, or the patient develops acute urinary retention, hydronephrosis, renal insufficiency, or recurrent urinary tract infections, or if the patient has postvoid residual urine volume >25% of the urinary bladder volume.

IX-64. The answer is B. *(Chap. 392)* Anabolic-androgenic steroid (AAS) use can cause increased erythropoiesis, and elevated hemoglobin and hematocrit can be clues to AAS. AAS abuse causes suppression of both luteinizing hormone (LH) and follicle-stimulating hormone (FSH) and subsequent testicular atrophy with reduction in testicular volumes. Observational studies inform us that AAS users have an increased mortality and morbidity when compared with the general population. However, the adverse effects of long-term AAS abuse remain poorly understood. Most of the information about the adverse effects of AAS has emerged from case reports, uncontrolled studies, or clinical trials that used replacement doses of testosterone. Of note, AAS users may administer 10–100 times the replacement doses of testosterone over many years, making it unjustifiable to extrapolate from trials using replacement doses. It is unclear what risk isolated AAS abuse carries. A substantial fraction of AAS users also use other drugs that are perceived to be muscle building or performance enhancing, such as growth hormone; erythropoiesis-stimulating agents; insulin; stimulants such as amphetamine, clenbuterol, cocaine, ephedrine, and thyroxine; and drugs perceived to reduce adverse effects such as human chorionic gonadotropin, aromatase inhibitors, or estrogen antagonists. The men who abuse AAS are more likely to engage in other high-risk behaviors than nonusers. The adverse events associated with AAS use may be due to AAS themselves, concomitant use of other drugs, high-risk behaviors, and host characteristics that may render these individuals more susceptible to AAS use or to other high-risk behaviors.

IX-65. The answer is E. *(Chap. 393)* Numerous studies highlight health disparities involving the care of lesbian, gay, bisexual, and transgender (LGBT) people. Lesbian and bisexual women are less likely to receive recommended preventive screenings such as breast, cervical, and colorectal cancer screenings. Among men who have sex with men, rates of human papillomavirus–associated anal cancers are 17 times higher than those of heterosexual men. In addition, gay and bisexual men accounted for 67% of all new HIV diagnoses in the United States in 2014, and they disproportionately contract sexually transmitted infections. In 2014, men who have sex with men accounted for 83% of primary and secondary syphilis infections in the United States where the sex of the sexual partner was known. Transgender individuals have a higher prevalence of HIV infection and suicide compared with other groups; 41% of transgender adults report ever attempting suicide compared with 1.6% of the general population. Research has found that LGBT individuals are more likely to experience depression, anxiety, and alcohol and drug use than their counterparts.

Most concerning are the rates of suicide attempts and ideation among the LGBT community, particularly youth. LGBT youth are more than twice as likely to attempt suicide than their heterosexual peers, and approximately 30% of LGBT students report having attempted suicide over a 12-month period. In addition, U.S. studies indicate that substance abuse is twice as common in LGBT youth compared with their counterparts.

IX-66. **The answer is A.** *(Chap. 393)* Addressing health disparities and creating positive health care experiences requires an understanding of the diversity of cultural expression and lives of LGBT persons (Table IX-66). Foremost, providers must be able to distinguish *gender identity* from *sexual orientation*. Gender identity is a person's internal sense of their gender. It should not be confused with sex assigned at birth, which is based on anatomy and biology. Gender identity expands beyond the binary male and female, and includes persons who think of their gender as containing elements of both or neither. Many individuals who do not identify with the gender that correlates with their sex assigned at birth often use the terms transgender or trans-male or trans-female to identify themselves. Sexual orientation refers to how one thinks of their physical or emotional attraction to others. Sexual orientation has three dimensions: attraction, behavior, and identity. Attraction refers to one's desire to be with someone, regardless of one's behavior or stated identity. For example, a woman may be attracted to another woman, but this attraction may never be acted on and may not form part of her sexual identity. Behavior refers to a person's sexual and romantic partners. Although sexual identity often aligns with behavior, some individuals who identify as heterosexual may have same-gender partners and some individuals who identify as lesbian or gay may have different-gender partners. Lastly, identity refers to how a person defines their own sexuality. Common terms for sexual identity include gay, lesbian, bisexual, straight, heterosexual, homosexual, and asexual. As individuals go through the process of understanding their sexuality and self-identity over time, they may change how they define their sexual identity.

IX-67. **The answer is E.** *(Chap. 394)* A number of complex human syndromes with defined inheritance are associated with obesity (Table IX-67). Although specific genes have limited definition at present, their identification may enhance our understanding of more common forms of human obesity. In the Prader-Willi syndrome, a multigenic neurodevelopmental disorder, obesity coexists with short stature, mental retardation, hypogonadotropic hypogonadism, hypotonia, small hands and feet, fish-shaped mouth, and hyperphagia. Most patients have reduced expression of imprinted paternally inherited genes encoded in the 15q11-13 chromosomal region. Reduced expression of Snord116, a small nucleolar RNA highly expressed in hypothalamus, may be an important cause of defective hypothalamic function in this disorder. Bardet-Biedl syndrome is a genetically heterogeneous disorder characterized by obesity, mental retardation, retinitis pigmentosa, diabetes, renal and cardiac malformations, polydactyly, and hypogonadotropic hypogonadism. Ahlstrom syndrome is associated with obesity in childhood but no intellectual disability. Obese patients commonly have central obesity, hypertension, and glucose intolerance; they lack other specific stigmata of Cushing syndrome. Patients with insulinoma often gain weight as a result of overeating to avoid hypoglycemic symptoms but do not have any other features described for this patient.

IX-68. **The answer is E.** *(Chap. 395)* Symptoms and diseases that are directly or indirectly related to obesity are listed in Table IX-68. Although individuals vary, the number and severity of organ-specific comorbid conditions usually rise with increasing levels of obesity. Patients at very high absolute risk include those with the following: established coronary heart disease; presence of other atherosclerotic diseases, such as peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease; type 2 diabetes; and sleep apnea. Ovarian cancer is not associated with obesity.

IX-69. **The answer is C.** *(Chap. 396)* The worldwide prevalence of diabetes mellitus (DM) has risen dramatically over the last two decades, from an estimated 30 million cases in 1985 to 415 million in 2017. Based on current trends, the International Diabetes Federation

TABLE IX-66 Common LGBT Terminology and Definitions

Term	Definition
Agender	Identifying as having no gender.
Asexual	Experiencing little or no sexual attraction to others.
Assigned sex at birth	The sex (male or female) assigned to a child at birth, most often based on the child's external anatomy. Also referred to as birth sex, natal sex, biological sex, or sex.
Bisexual	A sexual orientation that describes a person who is emotionally and sexually attracted to people of their own gender and people of other genders.
Cisgender	A person whose gender identity and assigned sex at birth correspond (i.e., a person who is not transgender).
Gay	A sexual orientation that describes a person who is emotionally and sexually attracted to people of their own gender. It can be used regardless of gender identity, but it is more commonly used to describe men.
Gender dysphoria	Distress experienced by some individuals whose gender identity does not correspond with their assigned sex at birth. Manifests as clinically significant distress or impairment in social, occupational, or other important areas of functioning.
Gender expression	The way a person acts, dresses, speaks, and behaves (i.e., feminine, masculine, androgynous). Gender expression does not necessarily correspond to assigned sex at birth or gender identity.
Gender identity	A person's internal sense of being a man/male, woman/female, both, neither, or another gender.
Gender nonconforming	Expressing a gender that differs from a given society's norms for males and females.
Heterosexual	A sexual orientation that describes women who are emotionally and sexually attracted to men, and men who are emotionally and sexually attracted to women.
Intersex (disorders of sexual development)	A group of rare conditions where the reproductive organs and genitals do not develop as expected.
Lesbian	A sexual orientation that describes a woman who is emotionally and sexually attracted to other women.
Men who have sex with men (MSM)/women who have sex with women (WSW)	Categories used in research and public health to describe those who engage in same-sex sexual behavior, regardless of their sexual orientation. Individuals rarely use the terms MSM or WSW to describe themselves.
Pangender	Describes a person whose gender identity comprises many genders.
Pansexual	A sexual orientation that describes a person who is emotionally and sexually attracted to people regardless of gender.
Queer	An umbrella term used by some to describe people who think of their sexual orientation or gender identity as outside of societal norms. Some people view the term as more fluid and inclusive than traditional categories for sexual orientation and gender identity. Due to its history as a derogatory term, it is not embraced or used by all members of the LGBT community.
Questioning	Describes an individual who is unsure about or is exploring their own sexual orientation and/or gender identity.
Same-sex attraction	Describes the experience of a person who is emotionally and/or sexually attracted to people of the same gender. Use of this term is not indicative of a person's sexual behavior.
Sexual orientation	Describes how a person characterizes their physical and emotional attraction to others. Sexual orientation is distinct from sex, gender identity, and gender expression.
Trans man/transgender man/female-to-male (FTM)	A transgender person whose gender identity is male may use these terms to describe themselves. Some will just use the term *man*.
Trans woman/transgender woman/male-to-female (MTF)	A transgender person whose gender identity is female may use these terms to describe themselves. Some will just use the term *woman*.
Transgender	Describes a person whose gender identity and assigned sex at birth do not correspond. Also used as an umbrella term to include gender identities outside of male and female.
Transition/affirmation	For transgender persons, the process of coming to recognize, accept, and express one's gender identity. Most often, this refers to the period when a person makes social, legal, and/or medical changes, such as changing their clothing, name, and sex designation, as well as using medical interventions.

Note: It is important to note that definitions vary across communities, that they change over time, and that not all LGBT people agree with all these definitions.

TABLE IX-67 **A Comparison of Syndromes of Obesity—Hypogonadism and Mental Retardation**

	Syndrome				
Feature	Prader-Willi	Laurence-Moon-Biedl	Ahlstrom	Cohen	Carpenter
Inheritance	Sporadic; two-thirds have defect	Autosomal recessive	Autosomal recessive	Probably autosomal recessive	Autosomal recessive
Stature	Short	Normal; infrequently short	Normal; infrequently short	Short or tall	Normal
Obesity	Generalized Moderate to severe Onset 1–3 years	Generalized Early onset, 1–2 years	Truncal Early onset, 2–5 years	Truncal Mid-childhood, age 5	Truncal, gluteal
Craniofacies	Narrow bifrontal diameter Almond-shaped eyes Strabismus V-shaped mouth High-arched palate	Not distinctive	Not distinctive	High nasal bridge Arched palate Open mouth Short philtrum	Acrocephaly Flat nasal bridge High-arched palate
Limbs	Small hands and feet Hypotonia	Polydactyly	No abnormalities	Hypotonia Narrow hands and feet	Polydactyly Syndactyly Genu valgum
Reproductive status	1° Hypogonadism	1° Hypogonadism	Hypogonadism in males but not in females	Normal gonadal function or hypogonadotropic hypogonadism	2° Hypogonadism
Other features	Enamel hypoplasia Hyperphagia Temper tantrums Nasal speech			Dysplastic ears Delayed puberty	
Mental retardation	Mild to moderate		Normal intelligence	Mild	Slight

projects that 642 million individuals will have diabetes by the year 2040 (see *http://www.idf.org/*). Although the prevalence of both type 1 and type 2 DM is increasing worldwide, the prevalence of type 2 DM is rising much more rapidly, presumably because of increasing obesity, reduced activity levels as countries become more industrialized, and the aging of the population. The incidence of type 1 diabetes has been increasing at a rate of 3–5% per year worldwide. The cause for this increase is not well understood, but type 1 DM is increasingly being diagnosed at younger ages. In 2015, the prevalence of diabetes in individuals aged 20–79 ranged from 7.2–11.4%. The countries with the greatest number of individuals with diabetes in 2015 are China (109.6 million), India (73 million), the United States (30.3 million), Brazil (14 million), and the Russian Federation (9 million). In the most recent estimate for the United States (2017), the Centers for Disease Control and Prevention estimated that 9.4% of the population had diabetes, and as many as 34% of U.S. adults had prediabetes. Approximately 25% of the individuals with diabetes in the United States were undiagnosed; globally, it is estimated that as many of 50% of individuals with diabetes may be undiagnosed. The prevalence of DM increases with age. In 2015, the prevalence of DM in the United Sates was estimated to be 0.25% in individuals age <20 years, 4.1% in persons aged 20–44 years, and 16.2% in persons 45–64 years old. In individuals aged >65 years, the prevalence of DM was 25.9%. Similar age-related trends have been observed worldwide. The prevalence of diabetes is similar among men and women, but diabetes-related mortality rates are higher in men compared with women.

TABLE IX-68 Obesity-Related Organ Systems Review

- **Cardiovascular**
  - Hypertension
  - Congestive heart failure
  - Cor pulmonale
  - Varicose veins
  - Pulmonary embolism
  - Coronary artery disease
- **Endocrine**
  - Metabolic syndrome
  - Type 2 diabetes
  - Dyslipidemia
  - Polycystic ovarian syndrome
- **Musculoskeletal**
  - Hyperuricemia and gout
  - Immobility
  - Osteoarthritis (knees and hips)
  - Low back pain
  - Carpal tunnel syndrome
- **Psychological**
  - Depression/low self-esteem
  - Body image disturbance
  - Social stigmatization
- **Integument**
  - Striae distensae
  - Stasis pigmentation of legs
  - Lymphedema
  - Cellulitis
  - Intertrigo, carbuncles
  - Acanthosis nigricans
  - Acrochordons (skin tags)
  - Hidradenitis suppurativa
- **Respiratory**
  - Dyspnea
  - Obstructive sleep apnea
  - Hypoventilation syndrome
  - Pickwickian syndrome
  - Asthma
- **Gastrointestinal**
  - Gastroesophageal reflux disease
  - Nonalcoholic fatty-liver disease
  - Cholelithiasis
  - Hernias
  - Colon cancer
- **Genitourinary**
  - Urinary stress incontinence
  - Obesity-related glomerulopathy
  - Hypogonadism (male)
  - Breast and uterine cancer
  - Pregnancy complications
- **Neurologic**
  - Stroke
  - Idiopathic intracranial hypertension
  - Meralgia paresthetica
  - Dementia

IX-70. **The answer is D.** *(Chap. 396)* Islet cell autoantibodies (ICAs) are a composite of several different antibodies directed at pancreatic islet molecules such as glutamic acid decarboxylase (GAD), *insulin*, IA-2/ICA-512, and ZnT-8, and serve as a marker of the autoimmune process of type 1 diabetes mellitus (DM). Assays for autoantibodies to GAD-65 and insulin are commercially available. Testing for ICAs can be useful in classifying the type of DM as type 1 and in identifying nondiabetic individuals at risk for developing type 1 DM. ICAs are present in the majority of individuals (>85%) diagnosed with new-onset type 1 DM, in a significant minority of individuals with newly diagnosed type 2 DM (5–10%), and occasionally in individuals with gestational diabetes mellitus (<5%). ICAs are present in 3–4% of first-degree relatives of individuals with type 1 DM. In combination with impaired insulin secretion after IV glucose tolerance testing, they predict a >50% risk of developing type 1 DM within 5 years. Increasing numbers of autoantibodies are associated with an increased risk of diabetes development. In children with multiple autoantibodies, ~70% developed type 1 DM after 10 years of follow-up, with 80% developing diabetes after 15-year of follow-up. At present, the measurement of ICAs in nondiabetic individuals remains a research tool because no treatments have been demonstrated to prevent the occurrence or progression to type 1 DM.

IX-71. **The answer is E.** *(Chap. 396)* Because the patient has symptoms, she is not being screened for diabetes mellitus. For screening, the fasting plasma glucose or hemoglobin A1c is recommended. Because the patient has symptoms, a random plasma glucose of >200 mg/dL is adequate to diagnose diabetes mellitus. Other criteria include fasting plasma glucose >126 mg/dL, hemoglobin A1c >6.4%, or 2-hour plasma glucose >200 mg/dL during an oral glucose tolerance test. C-peptide is a useful tool to determine whether the normal cleavage of insulin from its precursor is occurring. A normal C-peptide level with hypoglycemia suggests surreptitious insulin use, and a low C-peptide level with hyperglycemia suggests pancreatic failure.

IX-72. **The answer is C.** *(Chap. 396)* Glucose tolerance is classified into three categories: normal glucose tolerance, impaired glucose homeostasis, and diabetes mellitus. Normal glucose tolerance is defined by the following: fasting plasma glucose <100 mg/dL, plasma glucose <140 mg/dL following an oral glucose challenge, and hemoglobin A1c <5.6%. Abnormal glucose homeostasis is defined as a fasting plasma glucose of 100–125 mg/dL or a plasma glucose of 140–199 following an oral glucose tolerance test or hemoglobin A1c of 5.7–6.4%. Actual diabetes mellitus is defined by either a fasting plasma glucose >126 mg/dL, glucose of 200 mg/dL after an oral glucose tolerance test, or hemoglobin A1c ≥6.5%.

IX-73. **The answer is D.** *(Chap. 396)* Individuals with type 2 diabetes mellitus (T2DM) often exhibit the following features: (1) develop diabetes after the age of 30 years; (2) are usually obese (80% are obese, but elderly individuals may be lean); (3) may not require insulin therapy initially; and (4) may have associated conditions such as insulin resistance, hypertension, cardiovascular disease, dyslipidemia, or polycystic ovary syndrome. In T2DM, insulin resistance is often associated with abdominal obesity (as opposed to hip and thigh obesity) and hypertriglyceridemia. Although most individuals diagnosed with T2DM are older, the age of diagnosis is declining, and there is a marked increase among overweight children and adolescents. The age of the patient should not be the sole basis for determining the type of diabetes present. Some individuals with phenotypic T2DM present with diabetic ketoacidosis but lack autoimmune markers and may be later treated with oral glucose-lowering agents rather than insulin (this clinical picture is sometimes referred to as ketosis-prone T2DM). Monogenic forms of diabetes (maturity-onset diabetes of the young) should be considered in those with diabetes onset at <30 years of age, an autosomal pattern of diabetes inheritance (which this patient lacks), and the lack of nearly complete insulin deficiency.

IX-74. **The answer is B.** *(Chap. 397)* Current insulin preparations are generated by recombinant DNA technology and consist of the amino acid sequence of human insulin or variations thereof to alter insulin absorption and hence insulin action (Table IX-74). Insulins can be classified as short-acting or long-acting. Insulin glargine is a long-acting biosynthetic human insulin that differs from normal insulin in that asparagine is replaced by glycine at amino acid 21, and two arginine residues are added to the C terminus of the B chain, leading to the formation of microprecipitates at physiologic pH in subcutaneous tissue. Compared with NPH insulin, the onset of insulin glargine action is later, the duration of action is longer (~24 hours), and there is a less pronounced peak. A lower incidence of hypoglycemia, especially at night, has been reported with insulin glargine when compared with NPH insulin. Lispro, aspart, and regular insulin are all short-acting formulations with shorter duration than glargine or NPH.

IX-75. **The answer is A.** *(Chap. 397)* Individuals with type 1 or type 2 diabetes mellitus (DM) and severe hyperglycemia (>13.9 mmol/L [250 mg/dL]) should be assessed for clinical stability, including mentation and hydration. Depending on the patient and the rapidity and duration of the severe hyperglycemia, an individual may require more intense and rapid therapy to lower the blood glucose. However, many patients with poorly controlled diabetes and hyperglycemia have few symptoms. The physician should assess if the patient is stable or if diabetic ketoacidosis (DKA) or a hyperglycemic hyperosmolar state (HHS) should be considered. DKA and HHS are acute, severe disorders directly related to diabetes. DKA was formerly considered a hallmark of type 1 DM, but also occurs in individuals with type 2 DM who can sometimes subsequently be treated with oral glucose-lowering agents (usually obese individuals of Hispanic or African American descent). HHS is primarily seen in individuals with type 2 DM. Both disorders are associated with absolute

TABLE IX-74 Properties of Insulin Preparations[a]

	Time of Action		
Preparation	Onset (h)	Peak (h)	Effective Duration (h)
Short-acting[b]			
Aspart	<0.25	0.5–1.5	2–4
Glulisine	<0.25	0.5–1.5	2–4
Lispro[f]	<0.25	0.5–1.5	2–4
Regular[g]	0.5–1.0	2–3	3–6
Inhaled human insulin	0.5–1.0	2–3	3
Long-acting[g]			
Degludec	1–9	—[c]	42[d]
Detemir	1–4	—[c]	12–24[d]
Glargine[f]	2–4	—[c]	20–24
NPH	2–4	4–10	10–16
Examples of insulin combinations[e]			
75/25–75% protamine lispro, 25% lispro	<0.25	Dual[f]	10–16
70/30–70% protamine aspart, 30% aspart	<0.25	Dual[f]	15–18
50/50–50% protamine lispro, 50% lispro	<0.25	Dual[f]	10–16
70/30–70% NPH, 30% regular	0.5–1	Dual[f]	10–16
Combination of long-acting insulin and glucagon-like peptide-1 receptor agonist	See text		

[a] Injectable insulin preparations (with exception of inhaled formulation) available in the United States; others are available in the United Kingdom and Europe.
[b] Formulation with niacinamide has a slightly more rapid onset and offset.
[c] Degludec, determir, and glargine have minimal peak activity.
[d] Duration is dose dependent.
[e] Other insulin combinations are available.
[f] Dual: two peaks—one at 2–3 h and the second one several hours later.
[g] Also available in concentrations >U-100.

or relative insulin deficiency, volume depletion, and acid-base abnormalities. DKA and HHS exist along a continuum of hyperglycemia, with or without ketosis. The metabolic similarities and differences in DKA and HHS are highlighted in Table IX-75. Patients with HHS typically have serum osmolality >330 mOsm/L and do not have a severe acidosis (pH >7.3 on arterial blood gas). Hyponatremia is less pronounced in HHS and ketosis is less common.

TABLE IX-75 Laboratory Values in Diabetic Ketoacidosis (DKA) and Hyperglycemic Hyperosmolar State (HHS) (Representative Ranges at Presentation)

	DKA	HHS
Glucose[a] (mmol/L; mg/dL)	13.9–33.3 (250–600)	33.3–66.6 (600–1200)
Sodium (mEq/L)	125–135	135–145
Potassium[a,b]	Normal to ↑	Normal
Magnesium[a]	Normal	Normal
Chloride[a]	Normal	Normal
Phosphate[a,b]	Normal	Normal
Creatinine	Slightly ↑	Moderately ↑
Osmolality (mOsm/mL)	300–320	330–380
Plasma ketones[a]	++++	+/−
Serum bicarbonate[a] (mEq/L)	<15	Normal to slightly ↓
Arterial pH	6.8–7.3	>7.3
Arterial PCO_2[a] (mmHg)	20–30	Normal
Anion gap[a] ($Na - [Cl + HCO_3]$)	↑	Normal to slightly ↑

[a] Large changes occur during treatment of DKA.
[b] Although plasma levels may be normal or high at presentation, total-body stores are usually depleted.

IX-76. The answer is A. *(Chap. 397)* As with any therapy, the benefits of efforts directed toward glycemic control must be balanced against the risks of treatment (Table IX-76). Side effects of intensive treatment include an increased frequency of serious hypoglycemia, weight gain, increased economic costs, and greater demands on the patient. In the Diabetes Control and Complications Trial (DCCT) quality of life was very similar in the intensive and standard therapy groups. The most serious complication of therapy for diabetes mellitus is hypoglycemia. Severe, recurrent hypoglycemia warrants examination of treatment regimen and glycemic goal for the individual patient. Weight gain occurs with most (insulin, insulin secretagogues, thiazolidinediones) but not all (metformin, α-glucosidase inhibitors, glucagon-like peptide-1 receptor agonists like exenatide, dipeptidyl peptidase-4 inhibitors) therapies. Hypoglycemia can occur with glimepiride and repaglinide so they would not be preferred in this patient. Exenatide would avoid the weight gain the patient is concerned about and hypoglycemia that the patient has experienced in the past.

IX-77. The answer is D. *(Chap. 397)* First-line oral therapy for patients with type 2 diabetes mellitus (T2DM) is metformin. It is contraindicated in patients with a glomerular filtration rate <60 mL/min, any form of acidosis, congestive heart failure, liver disease, or severe hypoxemia, but is well tolerated in most individuals. Insulin secretagogues, biguanides, α-glucosidase inhibitors, thiazolidinediones, GLP-1 agonists, dipeptidyl peptidase-4 (DPP-IV) inhibitors, and insulin have all been approved as monotherapy for T2DM. Because of extensive clinical experience, favorable side effect profile, and relatively low cost, metformin is the recommended first-line agent. It has additional benefits of promotion of mild weight loss, lower insulin levels, and mild improvements in lipid profile. Sulfonylureas such as glyburide, GLP-1 agonists such as exenatide, and insulin DPP-IV inhibitors such as sitagliptin may be appropriate as combination therapy but are not considered first-line therapy for most patients.

IX-78. The answer is A. *(Chap. 397)* Diabetic ketoacidosis is an acute complication of diabetes mellitus. It results from a relative or absolute deficiency of insulin combined with a counterregulatory hormone excess. In particular, a decrease in the ratio of insulin to glucagons promotes gluconeogenesis, glycogenolysis, and the formation of ketone bodies in the liver. Ketosis results from an increase in the release of free fatty acids from adipocytes, with a resultant shift toward ketone body synthesis in the liver. This is mediated by the relationship between insulin and the enzyme carnitine palmitoyl transferase I. At physiologic pH, ketone bodies exist as ketoacids, which are neutralized by bicarbonate. As bicarbonate stores are depleted, acidosis develops. Clinically, these patients have nausea, vomiting, and abdominal pain. They are dehydrated and may be hypotensive. Lethargy and severe central nervous system depression may occur. The treatment centers on replacement of the body's insulin, which will result in cessation of the formation of ketoacids and improvement of the acidotic state. Assessment of the level of acidosis may be done with an arterial blood gas. These patients have an anion gap acidosis and often a concomitant metabolic alkalosis resulting from volume depletion. Volume resuscitation with IV fluids is critical. Many electrolyte abnormalities may occur. Total-body sodium, potassium, and magnesium are depleted in these patients. As a result of the acidosis, intracellular potassium may shift out of cells and cause a normal or even elevated potassium level. However, with improvement in the acidosis, the serum potassium rapidly falls. Therefore, potassium repletion is critical despite the presence of a "normal" level. Because of the osmolar effects of glucose, fluid is drawn into the intravascular space. This results in a drop in the measured serum sodium. There is a drop of 1.6 mEq/L in serum sodium for each rise of 100 mg/dL in serum glucose. In this case, the serum sodium will improve with hydration alone. The use of 3% saline is not indicated because the patient has no neurologic deficits, and the expectation is for rapid resolution with IV fluids alone.

IX-79. The answer is D. *(Chap. 397)* Virtually all medical and surgical subspecialties are involved in the care of hospitalized patients with diabetes. Hyperglycemia, whether in a patient with known diabetes or in someone without known diabetes, appears to be a predictor of poor outcome in hospitalized patients. General anesthesia, surgery, infection, or concurrent illness raises the levels of counterregulatory hormones (cortisol, growth hormone,

TABLE IX-76 Agents Used for Treatment of Type 1 or Type 2 Diabetes

	Mechanism of Action	Examples[a]	HbA1c Reduction (%)[b]	Agent-Specific Advantages	Agent-Specific Disadvantages	Contraindications
Oral						
Biguanides[c*]	↓ Hepatic glucose production	Metformin	1–2	Weight neutral, do not cause hypoglycemia, inexpensive, extensive experience, ↓ CV events	Diarrhea, nausea, lactic acidosis, vitamin B_{12} deficiency	Renal insufficiency (see text for GFR <45 mL/min), CHF, radiographic contrast studies, hospitalized patients, acidosis
α-Glucosidase inhibitors[c**]	↓ GI glucose absorption	Acarbose, miglitol, voglibose	0.5–0.8	Reduce postprandial glycemia	GI flatulence, liver function tests	Renal/liver disease
Dipeptidyl peptidase IV inhibitors[c***]	Prolong endogenous GLP-1 action; ↑ insulin, ↓ glucagon	Alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin	0.5–0.8	Well tolerated, do not cause hypoglycemia	Angioedema/urticarial and immune-mediated dermatologic effects	Reduced dose with renal disease
Insulin secretagogues: sulfonylureas[c*]	↑ Insulin secretion	Glibornuride, gliclazide, glimepiride, glipizide, gliquidone, glyburide, glyclopyramide	1–2	Short onset of action, lower postprandial glucose, inexpensive	Hypoglycemia, weight gain	Renal/liver disease
Insulin secretagogues: non-sulfonylureas[c***]	↑ Insulin secretion	Mitiglinide nateglinide, repaglinide	0.5–1.0	Short onset of action, lower postprandial glucose	Hypoglycemia	Renal/liver disease
Sodium-glucose cotransporter 2 inhibitors[***]	↑ Renal glucose excretion	Canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	0.5–1.0	Do not cause hypoglycemia, ↓ weight and BP; see text for CVD effect	Urinary and genital infections, polyuria, dehydration, exacerbate tendency to hyperkalemia and DKA; see text	Moderate renal insufficiency, insulin-deficient DM
Thiazolidinediones[c***]	↓ Insulin resistance, ↑ glucose utilization	Pioglitazone, rosiglitazone	0.5–1.4	Lower insulin requirements	Peripheral edema, CHF, weight gain, fractures, macular edema	CHF, liver disease
Parenteral						
Amylin agonists[c,d***]	Slow gastric emptying, ↓ glucagon	Pramlintide	0.25–0.5	Reduce postprandial glycemia, weight loss	Injection, nausea, ↑ risk of hypoglycemia with insulin	Agents that also slow GI motility
GLP-1 receptor agonists[c***]	↑ Insulin, ↓ glucagon, slow gastric emptying, satiety	Albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide	0.5–1.0	Weight loss, do not cause hypoglycemia; see text for CVD effect	Injection, nausea, ↑ risk of hypoglycemia with insulin secretagogues	Renal disease, agents that also slow GI motility; medullary carcinoma of thyroid, pancreatic disease
Insulin[c,d****]	↑ Glucose utilization, ↓ hepatic glucose production, and other anabolic actions	See text and Table IX-74	Not limited	Known safety profile	Injection, weight gain, hypoglycemia	
Medical nutrition therapy and physical activity[c*]	↓ Insulin resistance, ↑ insulin secretion	Low-calorie, low-fat diet, exercise	1–3	Other health benefits	Compliance difficult, long-term success low	

[a] Examples are approved for use in the United States; others are available in other countries. Examples may not include all agents in the class.

[b] HbA1c reduction (absolute) depends partly on starting HbA1c.

[c] Used for treatment of type 2 diabetes.

[d] Used in conjunction with insulin for treatment of type 1 diabetes. Cost of agent in the United States: [*]low, [**]moderate, [***]high, [****]variable.

Note: Some agents used to treat type 2 DM are not included in table.

Abbreviations: BP, blood pressure; CHF, congestive heart failure; CV, cardiovascular; DKA, diabetic ketoacidosis; DM, diabetes mellitus; GFR, glomerular filtration rate; GI, gastrointestinal; HbA1c, hemoglobin A1c.

catecholamines, and glucagon) and cytokines that may lead to transient insulin resistance and hyperglycemia. In a number of cross-sectional studies of patients with diabetes, a greater degree of hyperglycemia was associated with worse cardiac, neurologic, and infectious outcomes. In some studies, patients who do not have pre-existing diabetes but who develop modest blood glucose elevations during their hospitalization appear to benefit from achieving near-normoglycemia using insulin treatment. However, a large randomized clinical trial Normoglycemia in Intensive Care Evaluation Survival Using Glucose Algorithm Regulation (NICESUGAR) of individuals in the intensive care unit (ICU; most of whom were receiving mechanical ventilation) found an increased mortality rate and a greater number of episodes of severe hypoglycemia with very strict glycemic control (target blood glucose of 4.5–6 mmol/L or 81–108 mg/dL) compared with individuals with a more moderate glycemic goal (mean blood glucose of 8 mmol/L or 144 mg/dL). Total parenteral nutrition (TPN) greatly increases insulin requirements. In addition, individuals not previously known to have diabetes may become hyperglycemic during TPN and require insulin treatment. Insulin infusions are preferred in the ICU or in a clinically unstable setting. The absorption of subcutaneous insulin may be variable in such situations. Insulin infusions can also effectively control plasma glucose in the perioperative period and when the patient is unable to take anything by mouth.

IX-80. **The answer is A.** *(Chap. 398)* Diabetic radiculopathy or polyradiculopathy is a syndrome characterized by severe disabling pain in the distribution of one or more nerve roots. It may be accompanied by motor weakness. Intercostal or truncal radiculopathy causes pain over the thorax or abdomen. Involvement of the lumbar plexus or femoral nerve may cause severe pain in the thigh or hip and may be associated with muscle weakness in the hip flexors or extensors (diabetic amyotrophy). Distal symmetric polyneuropathy is the most common form of diabetic neuropathy, most frequently presenting with distal sensory loss and pain, but up to 50% of patients do not have symptoms of neuropathy. Symptoms may include a sensation of numbness, tingling, sharpness, or burning that begins in the feet and spreads proximally. Meralgia paresthetica only involves sensory changes and would not cause motor weakness. Herniation of a disk and vertebral compression fractures can cause a radiculopathy and would be visualized on the MRI.

IX-81. **The answer is D.** *(Chap. 398)* Diabetes-related complications can be divided into vascular and nonvascular complications and are similar for type 1 and type 2 diabetes mellitus (DM) (Table IX-81). The vascular complications of DM are further subdivided into microvascular (retinopathy, macular edema, neuropathy, nephropathy) and macrovascular complications (coronary heart disease, peripheral arterial disease, cerebrovascular disease). Microvascular complications are diabetes specific, whereas macrovascular complications have pathophysiologic features that are both shared with the general population and diabetes specific. Nonvascular complications include infections, skin changes, cheiroarthropathy, and hearing loss. Some studies suggest that type 2 DM increases the risk of dementia and impaired cognitive function.

IX-82. **The answer is C.** *(Chap. 398)* The funduscopic examination demonstrates diabetic retinopathy with scattered hemorrhages, yellow exudates, and neovascularization proliferating from the optic disc. Diabetic retinopathy is the leading cause of blindness in individuals between the ages of 20 and 74 in the United States. Individuals with diabetes are 25 times more likely to go legally blind than individuals without diabetes. Diabetic retinopathy is classified into two stages: nonproliferative and proliferative. Nonproliferative retinopathy typically appears late in the first decade or early in the second decade of the disease. Characteristic findings include cotton wool spots, blot hemorrhages, and retinal vascular microaneurysms. Mild proliferative retinopathy may progress to more extensive disease, characterized by changes in venous vessel caliber, intraretinal microvascular abnormalities, and more numerous microaneurysms and hemorrhages. Pathophysiologically, there is loss of retinal pericytes, increased retinal vascular permeability, alterations in retinal blood flow, and abnormal retinal microvasculature. Severe nonproliferative diabetic retinopathy creates retinal hypoxemia and establishes the environment for development of proliferative retinopathy. Neovascularization, as shown in this patient's fundus, is the

TABLE IX-81 Diabetes-Related Complications

- Microvascular
  - Eye disease
    - Retinopathy (nonproliferative/proliferative)
    - Macular edema
  - Neuropathy
    - Sensory and motor (mono- and polyneuropathy)
    - Autonomic
  - Nephropathy (albuminuria and declining renal function)
- Macrovascular
  - Coronary heart disease
  - Peripheral arterial disease
  - Cerebrovascular disease
- Other
  - Gastrointestinal (gastroparesis, diarrhea)
  - Genitourinary (uropathy/sexual dysfunction)
  - Dermatologic
  - Infectious
  - Cataracts
  - Glaucoma
  - Cheiroarthropathy[a]
  - Periodontal disease
  - Hearing loss
- Other comorbid conditions associated with diabetes (relationship to hyperglycemia is uncertain): depression, obstructive sleep apnea, fatty liver disease, hip fracture, osteoporosis (in type 1 diabetes), cognitive impairment or dementia, low testosterone in men.

[a] Thickened skin and reduced joint mobility.

hallmark of proliferative retinopathy. Neovascular vessels typically appear at the optic disc as in this case. The most effective therapy for the treatment of diabetic retinopathy is prevention with intensive glycemic and blood pressure control. However, in established diabetic retinopathy, improved glycemic control leads to transient worsening of the disease. When proliferative retinopathy and neovascularization are present, retinal laser photocoagulation is required.

IX-83. **The answer is D.** *(Chap. 398)* Diabetes mellitus is the most common cause of chronic kidney disease, end-stage renal disease, and chronic kidney disease requiring renal replacement therapy. In the first 5 years after diabetes onset, glomerular hyperfiltration and increased glomerular filtration rate are seen. The glomerular basement membrane subsequently thickens, with concomitant mesangial volume and glomerular hypertrophy. Typically within 5–10 years, many individuals will begin to excrete small amounts of albumin in their urine. It is recommended to screen for albumin excretion annually with a 24-hour collection or spot albumin-to-creatinine ratio. Microalbuminuria is defined as >30–299 g/d in a 24-hour collection or 30–299 g/mg creatinine in a spot collection. However, interpretation may be clouded by conditions known to transiently increase albumin excretion including urinary tract infection, hematuria, heart failure, febrile illness, severe hyperglycemia (option B), severe hypertension (option E), pregnancy, and vigorous exercise (option C). If testing is positive, it should be repeated within 3–6 months, and treatment should begin at that time. This makes option A too soon for repeat testing and option D the most appropriate answer to the question. Although direct comparisons have not been done, experts believe that angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are equivalent in the treatment of albuminuria and diabetic nephropathy.

IX-84. **The answer is A.** *(Chap. 399)* The concept of hypoglycemia-associated autonomic failure in diabetes posits that recent antecedent iatrogenic hypoglycemia (or sleep or prior exercise) causes both defective glucose counterregulation (by reducing the epinephrine response to a given level of subsequent hypoglycemia in the setting of absent insulin and glucagon responses) and hypoglycemia unawareness (by reducing the sympathoadrenal response to a given level of subsequent hypoglycemia). These impaired responses create a vicious cycle of recurrent iatrogenic hypoglycemia. Hypoglycemia unawareness and, to some extent, the reduced epinephrine component of defective glucose counterregulation are reversible by as little as 2–3 weeks of scrupulous avoidance of hypoglycemia in most affected patients. On the basis of this pathophysiology, additional risk factors for hypoglycemia in diabetes include (1) absolute insulin deficiency, indicating that insulin levels will not decrease and glucagon levels will not increase as plasma glucose levels fall; (2) a history of severe hypoglycemia or of hypoglycemia unawareness, implying recent antecedent hypoglycemia, as well as prior exercise or sleep, indicating that the sympathoadrenal response will be attenuated; (3) impaired renal function resulting in reduced clearance of exogenous and endogenous insulin; (4) classical diabetic autonomic neuropathy; and (5) lower hemoglobin A1c (HBA1c), or lower glycemic goals even at elevated HBA1c levels (8–10%), as they represent an increased probability of recent antecedent hypoglycemia. Coronary artery disease is not associated with the risk for hypoglycemia.

IX-85. The answer is B. *(Chap. 399)* Maintenance of euglycemia involves a number of systems to lower elevated blood glucose and to restore normal levels when hypoglycemia is present or impending. This is particularly important for neurologic functioning because the brain cannot synthesize glucose and has only a few minutes' supply stored as glycogen. In a nondiabetic individual, the normal fasting plasma glucose level is normally tightly controlled between 70 and 110 mg/dL. When the plasma glucose begins to fall below about 80–85 mg/dL, the first line of defense to protect against development of hypoglycemia is to decrease insulin secretion. When this occurs, hepatic glycogenolysis and gluconeogenesis increase. In addition, lowered insulin levels lead to decreased peripheral glucose utilization. If the glucose continues to fall to about 65–70 mg/dL, other protective mechanisms are employed. The second line of defense against hypoglycemia is glucagon secretion, which further stimulates hepatic gluconeogenesis. Epinephrine may also be secreted, although it is not normally critical unless glucagon is deficient. Cortisol and growth hormone are secreted later in the pathway when hypoglycemia is prolonged greater than 4 hours. These hormones have no role in acute hypoglycemia.

IX-86. The answer is D. *(Chap. 399)* The patient presents with recurrent episodes of hypoglycemia that meet the Whipple triad of symptoms: (1) symptoms of hypoglycemia, (2) low plasma glucose concentration measured with a precise method (not a glucose monitor), and (3) relief of symptoms with raising the plasma glucose level. The differential starts with measuring insulin levels during hypoglycemia. The levels must be obtained during an episode to be interpretable. If insulin is elevated, it suggests either endogenous hyperproduction from an insulin-secreting tumor or exogenous administration causing factitious hypoglycemia. Because C-peptide is cleaved from native proinsulin to make the secreted product, it will be high in the case of endogenous hyperinsulinemia and will be low during an episode of factitious hypoglycemia. Surreptitious ingestion of sulfonylurea could cause hypoglycemia along with high insulin and C-peptide levels since the drug stimulates pancreatic insulin secretion. In this case, a sulfonylurea drug screen would be indicated. Red flags in this case that point to surreptitious insulin use include the patient being a health care worker and the presence of symptoms only at work. Other groups in which this is common are relatives of patients with diabetes and patients with a history of other factitious disorders. It is possible that the patient has an insulin-secreting β-cell tumor, but this is much less likely, and symptoms would be present during times other than work. Evaluation is aimed at demonstrating that pancreatic insulin secretion is suppressed during the episode of hypoglycemia. Although a failure of counterregulatory hormones can produce hypoglycemia, this is a rare cause of hypoglycemia, and evaluation should be aimed at this only after surreptitious use is ruled out.

IX-87. The answer is E. *(Chap. 400)* Secondary causes of dyslipidemia are diverse (Table IX-87). Severe hepatitis and liver failure are associated with dramatic reductions in plasma cholesterol, including low-density lipoprotein (LDL), and triglycerides due to reduced

TABLE IX-87 Secondary Causes of Dyslipidemia

LDL		HDL					
Elevated	Reduced	Elevated	Reduced	VLDL Elevated	IDL Elevated	Chylomicrons Elevated	Lp(a) Elevated
Hypothyroidism Nephrotic syndrome Cholestasis Acute intermittent porphyria Anorexia nervosa Hepatoma Drugs: thiazides, cyclosporin, carbamazepine	Severe liver disease Malabsorption Malnutrition Gaucher disease Chronic infectious disease Hyperthyroidism Drugs: niacin toxicity	Alcohol Exercise Exposure to chlorinated hydrocarbons Drugs: estrogen	Smoking DM type 2 Obesity Malnutrition Gaucher disease Cholesteryl ester storage disease Drugs: anabolic steroids, beta blockers	Obesity DM type 2 Glycogen storage disease Nephrotic syndrome Hepatitis Alcohol Renal failure Sepsis Stress Cushing syndrome Pregnancy Acromegaly Lipodystrophy Drugs: estrogen, beta blockers, glucocorticoids, bile acid binding resins, retinoic acid	Multiple myeloma Monoclonal gammopathy Autoimmune disease Hypothyroidism	Autoimmune disease DM type 2	Chronic kidney disease Nephrotic syndrome Inflammation Menopause Orchidectomy Hypothyroidism Acromegaly Drugs: growth hormone, isotretinoin

Abbreviations: DM, diabetes mellitus; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; Lp(a), lipoprotein A; VLDL, very-low-density lipoprotein.

lipoprotein biosynthetic capacity. Cholestasis is often associated with hypercholesterolemia. A major pathway by which cholesterol is excreted from the body is via secretion into bile, either directly or after conversion to bile acids, and cholestasis blocks this critical excretory pathway. Anorexia nervosa, hypothyroidism, and nephrotic syndrome can also lead to elevated levels of LDL.

IX-88. The answer is B. *(Chap. 400)* Proprotein convertase subtilisin/kexin type 9 (PCSK9) is an enzyme that modulates lipoprotein metabolism. PCSK9 inhibitors like evolocumab are antibodies that bind to circulating PCSK9 and prevent its interaction with the low-density lipoprotein (LDL) receptor. This permits more LDL receptors to recycle back to the cell surface and functionally increases the number of LDL receptors available to remove LDL from the blood. PCSK9 inhibitors are highly effective in lowering low-density lipoprotein cholesterol (LDL-C), with a mean 50–60% reduction in LDL-C (Table IX-88). They also reduce plasma levels of lipoprotein a modestly. PCSK9 inhibition has been proven to reduce cardiovascular events in patients with existing coronary heart disease. These antibodies are administered subcutaneously every 2–4 weeks. They are generally well tolerated, with the major side effect being injection site reactions. The mean reduction in plasma LDL-C on ezetimibe (10 mg) is 18%. Gemfibrozil and omega-3 fatty acids are useful in hypertriglyceridemia but not to lower LDL. Cholestyramine lowers LDL but can raise triglyceride levels.

IX-89. The answer is A. *(Chap. 400)* Lipoprotein lipase (LPL) deficiency is a very rare autosomal recessive disorder that results in elevated fasting triglyceride levels because the absence of LPL results in the inability of chylomicrons to undergo hydrolysis of triglycerides. Thus, circulating levels of chylomicrons, very-low-density lipoprotein, and triglycerides are high. Fasting triglyceride levels are typically >1000 mg/dL. LPL deficiency has an incidence of approximately 1 in 1,000,000 in the population. The disease typically presents in childhood or young adulthood with recurrent episodes of pancreatitis. Ophthalmologic examination may show lipemia retinalis with an opalescent appearance to the retinal blood vessels. Eruptive xanthomas are small, yellowish-white papules and may appear on the back, buttocks, and extensor surfaces of the arms and legs. Hepatosplenomegaly occurs because of uptake of the circulating chylomicrons by the reticuloendothelial system.

TABLE IX-88 Summary of the Major Approved Drugs Used for the Treatment of Dyslipidemia

Drug	Major Indications	Starting Dose	Maximal Dose	Mechanism	Common Side Effects
HMG-CoA reductase inhibitors (statins)	Elevated LDL-C; increased CV risk			↓ Cholesterol synthesis, ↑ Hepatic LDL receptors, ↓ VLDL production	Myalgias and myopathy ↑ Transaminases, ↑ Diabetes risk
Lovastatin		20–40 mg daily	80 mg daily		
Pravastatin		40–80 mg daily	80 mg daily		
Simvastatin		20–40 mg daily	80 mg daily		
Fluvastatin		20–40 mg daily	80 mg daily		
Atorvastatin		20–40 mg daily	80 mg daily		
Rosuvastatin		5–20 mg daily	40 mg daily		
Pitavastatin		1–2 mg daily	4 mg daily		
Cholesterol absorption inhibitor	Elevated LDL-C			↓ Cholesterol absorption, ↑ LDL receptors	Elevated transaminases
Ezetimibe		10 mg daily	10 mg daily		
Bile acid sequestrants	Elevated LDL-C			↑ Bile acid excretion and ↑ LDL receptors	Bloating, constipation, elevated triglycerides
Cholestyramine		4 g daily	32 g daily		
Colestipol		5 g daily	40 g daily		
Colesevelam		3750 mg daily	4375 mg daily		
PCSK9 inhibitors Evolocumab Alirocumab	Elevated LDL-C	140 mg SC q 2 weeks 75 mg SC q 2 weeks	420 mg SC q 1 month (HoFH) 150 mg SC q 2 weeks	↓ PCSK9 activity, ↑ LDL receptors	Injection site reactions
MTP inhibitor Lomitapide	HoFH	5 mg daily	60 mg daily	↓ VLDL production	Nausea, diarrhea, increased hepatic fat
ApoB inhibitor Mipomersen	HoFH	200 mg SC weekly	200 mg SC weekly	↓ VLDL production	Injection site reactions, flu-like symptoms, increased hepatic fat
Fibric acid derivatives Gemfibrozil Fenofibrate	Elevated TG	600 mg bid 145 mg qd	600 mg bid 145 mg qd	↑ LPL, ↓ VLDL synthesis	Dyspepsia, myalgia, gallstones, elevated transaminases
Omega-3 fatty acids Omega-3 acid ethyl esters	Elevated TG	4 g daily	4 g daily	↑ TG catabolism	Dyspepsia, fishy odor to breath
Icosapent ethyl		4 g daily	4 g daily		

Abbreviations: CV, cardiovascular; HoFH, homozygous familial hypercholesterolemia; LDL, low-density lipoprotein; LDL-C, LDL-cholesterol; LPL, lipoprotein lipase; MTP, microsomal triglyceride transfer protein; PCSK9: proprotein convertase subtilisin/kexin type 9; TG, triglyceride; VLDL, very-low-density lipoprotein.

Primary treatment of the disorder is to restrict dietary fat to 15 g/d or less. If dietary fat restriction alone is not sufficient to control the triglyceride level, fish oil has been useful in some patients.

IX-90. The answer is D. *(Chap. 400)* Familial hypercholesterolemia (FH) is the most common inherited cause of hypercholesterolemia and may be one of the most common single-gene disorders in humans. The incidence of the mutation that causes FH is estimated to be as common as 1 in 250 to 1 in 500 individuals in the population. FH is also known as autosomal dominant hypercholesterolemia, type 1, and is caused by loss-of-function mutations in the gene encoding the low-density lipoprotein (LDL) receptor. More than 1600 mutations in the gene have been reported. In the presence of a single mutation (heterozygous FH), there is a decrease of LDL receptors in the liver with a resulting decrease in clearance of LDL from the circulation, and plasma levels of LDL cholesterol typically range from 200–400 mg/dL. In the presence of two mutations (homozygous FH), LDL receptors are markedly reduced or absent. In these patients, the LDL cholesterol levels are markedly elevated to 400 to >1000 mg/dL. Many individuals with homozygous FH present with cutaneous xanthomas in childhood and early cardiovascular disease in late childhood or young adulthood. Although heterozygous patients have hypercholesterolemia from birth, disease recognition is usually not until adulthood when patients are found to have tendon xanthomas or coronary artery disease. In patients with heterozygous disease, there is generally a family history on at least one side of the family. Familial defective apolipoprotein (apo) B-100 has a similar presentation but is less common (1/1000). ApoA-V deficiency presents with xanthomas, but also pancreatitis and hepatosplenomegaly with elevated chylomicrons and very-low-density lipoprotein. Familial hepatic lipase deficiency and lipoprotein lipase deficiency are associated with increased chylomicrons, not LDL cholesterol, and present with eruptive xanthomas, hepatosplenomegaly, and pancreatitis. These conditions occur rarely (<1/1,000,000).

IX-91. **The answer is A.** *(Chap. 401)* In addition to the features specifically used to define the metabolic syndrome, other metabolic alterations are secondary to, or accompany insulin resistance (Table IX-91). Those alterations include increases in apolipoprotein (apo) B and apoC-III, uric acid, prothrombotic factors (fibrinogen, plasminogen activator inhibitor 1), serum viscosity, asymmetric dimethylarginine, homocysteine, white blood cell count, proinflammatory cytokines, C-reactive protein, increased urine albumin/creatinine ratio, nonalcoholic fatty liver disease and/or nonalcoholic steatohepatitis, polycystic ovary syndrome, and obstructive sleep apnea. Hyperuricemia from metabolic syndrome can lead to gout. There is no clear association with Alzheimer's disease.

TABLE IX-91 NCEP:ATPIII[a] 2001 and Harmonizing Definition Criteria for the Metabolic Syndrome

<table>
<tr><th>NCEP:ATPIII 2001</th><th colspan="3">Harmonizing Definition[b]</th></tr>
<tr><td rowspan="6">Three or more of the following:
• Central obesity: waist circumference >102 cm (M), >88 cm (F)
• Hypertriglyceridemia: triglyceride level ≥150 mg/dL or specific medication
• Low HDL cholesterol: <40 mg/dL and <50 mg/dL for men and women, respectively, or specific medication
• Hypertension: blood pressure ≥130 mmHg systolic or ≥85 mmHg diastolic or specific medication
• Fasting plasma glucose level ≥100 mg/dL or specific medication or previously diagnosed type 2 diabetes</td><td colspan="3">Three of the following:
Waist circumference (cm)</td></tr>
<tr><td>Men</td><td>Women</td><td>Ethnicity</td></tr>
<tr><td>≥94</td><td>≥80</td><td>Europid, sub-Saharan African, Eastern and Middle Eastern</td></tr>
<tr><td>≥90</td><td>≥80</td><td>South Asian, Chinese, and ethnic South and Central American</td></tr>
<tr><td>≥85</td><td>≥90</td><td>Japanese</td></tr>
<tr><td colspan="3">• Fasting triglyceride level >150 mg/dL or specific medication
• HDL cholesterol level <40 mg/dL and <50 mg/dL for men and women, respectively, or specific medication
• Blood pressure >130 systolic or >85 diastolic or previous diagnosis or specific medication
• Fasting plasma glucose level ≥100 mg/dL (alternative indication: drug treatment of elevated glucose levels)</td></tr>
</table>

[a] National Cholesterol Education Program and Adult Treatment Panel III.
[b] In this analysis, the following thresholds for waist circumference were used: white men, ≥94 cm; African American men, ≥94 cm; Mexican American men, ≥90 cm; white women, ≥80 cm; African American women, ≥80 cm; Mexican American women, ≥80 cm. For participants whose designation was "other race—including multiracial," thresholds that were once based on Europoid cutoffs (≥94 cm for men and ≥80 cm for women) and on South Asian cutoffs (≥90 cm for men and ≥80 cm for women) were used. For participants who were considered "other Hispanic," the International Diabetes Federation thresholds for ethnic South and Central Americans were used.
Abbreviations: F, female; HDL, high-density lipoprotein, M, male.

IX-92. **The answer is B.** *(Chap. 401)* Metabolic syndrome is a common disorder that features central obesity, hypertriglyceridemia, low levels of high-density lipoprotein cholesterol, hyperglycemia, and hypertension. The prevalence of the disease varies around the world, reflecting the age, ethnicity, and varying diagnostic criteria applied. The highest prevalence of metabolic syndrome worldwide occurs in the Native American populations in the United States, with nearly 60% of women age 45–49 and 45% of men age 45–49 being affected. In the United States, African American men are less commonly affected, whereas Mexican American women are more commonly affected. In France, the disease prevalence is generally the lowest in the world, with <10% of individuals between 30 and 60 years of age affected, although after age 60, the prevalence rises to 17.5%. Risk factors that confer increasing likelihood of developing metabolic syndrome include overweight/obesity, aging, sedentary lifestyle, diabetes mellitus, cardiovascular disease, and lipodystrophy. Central obesity is both a risk factor and a feature central to defining the presence of the disease. Central obesity as measured by waist circumference, not body mass index, is most strongly associated with insulin resistance and risk of diabetes mellitus and cardiovascular disease. The precise waist circumference at which the risk increases may vary between men and women and across different ethnicities. For instance, in Japanese women, the waist circumference that is used for diagnosis of metabolic syndrome is 90 cm compared with 85 cm for men. However, in individuals of Europoid descent, women are diagnosed with metabolic syndrome at a waist circumference ≥80 cm, whereas men are diagnosed at a waist circumference ≥94 cm. Aging is also associated with increased risk of metabolic syndrome. Metabolic syndrome affects about half of the population older than age 50, and after age 60, women are more affected than men. Physical inactivity is a predictor of cardiovascular events and death in individuals with metabolic syndrome. Spending more than 4 hours a day watching television or videos or using a computer confers a twofold greater risk of metabolic syndrome. Insulin resistance is felt to be the pathophysiologic hallmark of the metabolic syndrome, and about 75% of individuals with type 2 diabetes mellitus (T2DM) or impaired glucose tolerance have metabolic syndrome. When these diseases coexist in an individual, there is a higher prevalence of cardiovascular disease than with T2DM or glucose tolerance alone.

IX-93. **The answer is D.** *(Chap. 402)* Resorption of bone is carried out mainly by *osteoclasts*, multinucleated cells that are formed by fusion of cells derived from the common precursor of macrophages and osteoclasts (Figure IX-93). Thus, these cells derive from the hematopoietic lineage, quite different from the mesenchymal cells that become osteoblasts. Multiple factors that regulate osteoclast development have been identified. RANK ligand, a member of the tumor necrosis factor family, is expressed on the surface of osteocytes, osteoblasts, and stromal fibroblasts. In a process involving cell-cell interactions, RANK ligand binds to the RANK receptor on osteoclast progenitors, stimulating osteoclast differentiation and activation. Denosumab is a monoclonal antibody targeting RANK

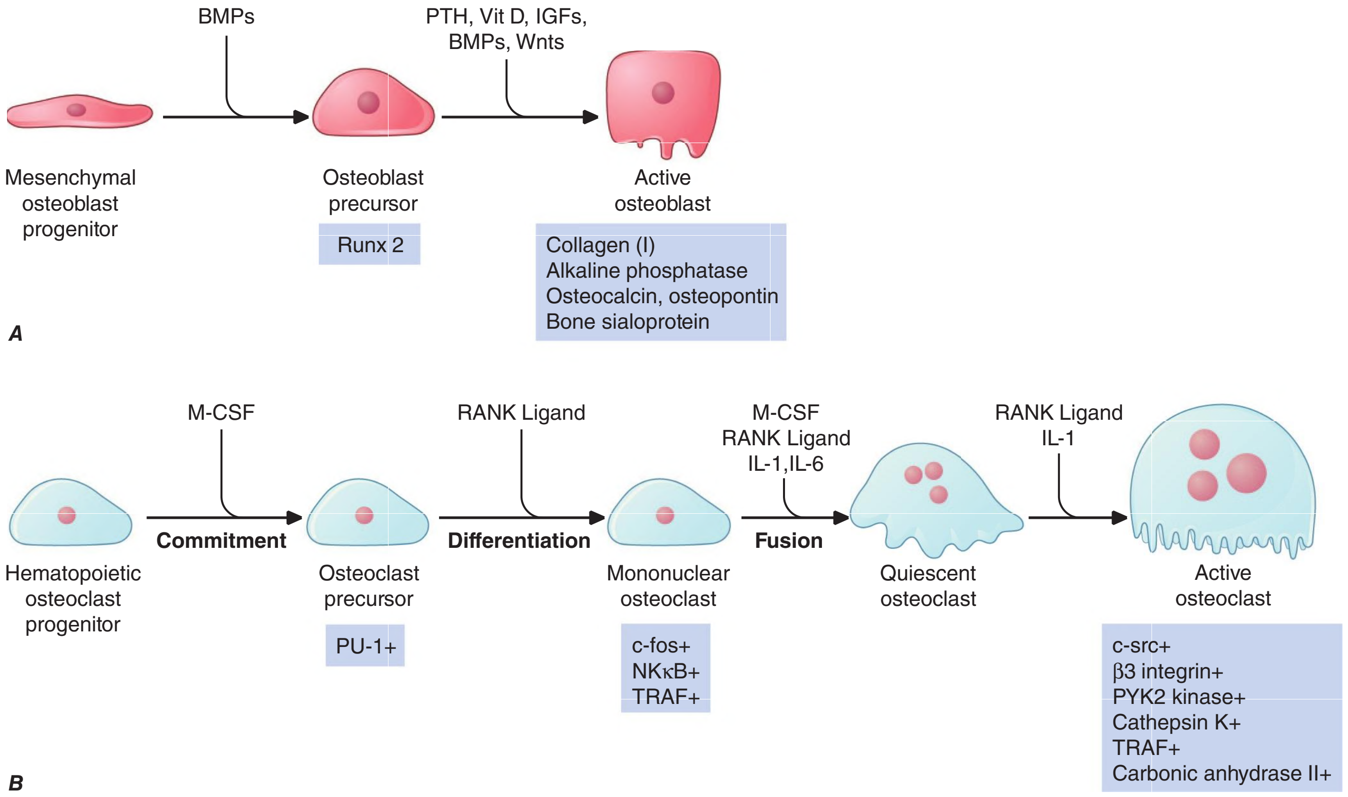

BMPs
PTH, Vit D, IGFs,
BMPs, Wnts
Mesenchymal osteoblast progenitor
Osteoblast precursor
Runx 2
Active osteoblast
Collagen (I)
Alkaline phosphatase
Osteocalcin, osteopontin
Bone sialoprotein
A
M-CSF
RANK Ligand
M-CSF
RANK Ligand
IL-1,IL-6
RANK Ligand
IL-1
Commitment
Differentiation
Fusion
Hematopoietic osteoclast progenitor
Osteoclast precursor
PU-1+
Mononuclear osteoclast
c-fos+
NKκB+
TRAF+
Quiescent osteoclast
Active osteoclast
c-src+
β3 integrin+
PYK2 kinase+
Cathepsin K+
TRAF+
Carbonic anhydrase II+
B

FIGURE IX-93 *Abbreviations:* BMP, bone morphogenetic protein; IGF, insulin growth factor; IL, interleukin; M-CSF, macrophage colony-stimulating factor; PTH, parathyroid hormone; vit D, vitamin D. (Modified with permission from Suda T et al: Modulation of osteoclast differentiation and function by the new members of the tumor necrosis factor receptor and ligand families. *Endocr Rev* 20:345, 1999.)

ligand. *Osteoblasts* synthesize and secrete the organic matrix and regulate its mineralization. They are derived from cells of mesenchymal origin. Osteocytes regulate osteoblasts partly by secreting a potent inhibitor of Wnt signaling called sclerostin. Numerous other growth-regulatory factors affect osteoblast function, including the three closely related transforming growth factor βs, fibroblast growth factors 2 and 18, platelet-derived growth factor, and insulin-like growth factors 1 and 2.

IX-94. The answer is C. *(Chap. 402)* Hypomagnesemia usually signifies substantial depletion of body magnesium stores (0.5–1 mmol/kg) (Table IX-94). Hypomagnesemia can result

TABLE IX-94 Causes of Hypomagnesemia

- I. Impaired intestinal absorption
  - A. Hypomagnesemia with secondary hypocalcemia (TRPM6 mutations)
  - B. Malabsorption syndromes
  - C. Vitamin D deficiency
  - D. Proton pump inhibitors
- II. Increased intestinal losses
  - A. Protracted vomiting/diarrhea
  - B. Intestinal drainage, fistulas
- III. Impaired renal tubular reabsorption
  - A. Genetic magnesium-wasting syndromes
    - 1. Gitelman syndrome
    - 2. Bartter syndrome
    - 3. Claudin 16 or 19 mutations
    - 4. Potassium channel mutations (Kv1.1, Kir4.1)
    - 5. Na^+,K^+-ATPase γ-subunit mutations (FXYD2)
  - B. Acquired renal disease
    - 1. Tubulointerstitial disease
    - 2. Postobstruction, ATN (diuretic phase)
    - 3. Renal transplantation
  - C. Drugs and toxins
    - 1. Ethanol
    - 2. Diuretics (loop, thiazide, osmotic)
    - 3. Cisplatin
    - 4. Pentamidine, foscarnet
    - 5. Cyclosporine
    - 6. Aminoglycosides, amphotericin B
    - 7. Cetuximab
  - D. Other
    - 1. Extracellular fluid volume expansion
    - 2. Hyperaldosteronism
    - 3. SIADH
    - 4. Diabetes mellitus
    - 5. Hypercalcemia
    - 6. Phosphate depletion
    - 7. Metabolic acidosis
    - 8. Hyperthyroidism
- IV. Rapid shifts from extracellular fluid
  - A. Intracellular redistribution
    - 1. Recovery from diabetic ketoacidosis
    - 2. Refeeding syndrome
    - 3. Correction of respiratory acidosis
    - 4. Catecholamines
  - B. Accelerated bone formation
    - 1. Post parathyroidectomy
    - 2. Treatment of vitamin D deficiency
    - 3. Osteoblastic metastases
  - C. Other
    - 1. Pancreatitis, burns, excessive sweating
    - 2. Pregnancy (third trimester) and lactation

Abbreviations: ATN, acute tubular necrosis; SIADH, syndrome of inappropriate antidiuretic hormone.

from intestinal malabsorption; protracted vomiting, diarrhea, or intestinal drainage; defective renal tubular magnesium reabsorption; or rapid shifts of magnesium from the extracellular fluid into cells, bone, or third spaces. Dietary magnesium deficiency is unlikely except possibly in the setting of alcoholism. A rare genetic disorder that causes selective intestinal magnesium malabsorption has been described (primary infantile hypomagnesemia). Another rare inherited disorder (hypomagnesemia with secondary hypocalcemia) is caused by mutations in the gene encoding TRPM6, a protein that, along with TRPM7, forms a channel important for both intestinal and distal-tubular renal transcellular magnesium transport. Malabsorptive states, often compounded by vitamin D deficiency, can critically limit magnesium absorption and produce hypomagnesemia despite the compensatory effects of secondary hyperparathyroidism and of hypocalcemia and hypomagnesemia to enhance cTAL magnesium reabsorption. Diarrhea or surgical drainage fluid may contain ≥5 mmol/L of magnesium. Proton pump inhibitors (omeprazole and others) may produce hypomagnesemia by an unknown mechanism that does not involve renal wasting of magnesium. Hyperthyroidism can cause hypomagnesemia as opposed to hypothyroidism.

IX-95. and IX-96. **The answers are A and C, respectively.** *(Chap. 402)* Hypophosphatemia results from one of three mechanisms: inadequate intestinal phosphate absorption, excessive renal phosphate excretion, and rapid redistribution of phosphate from the extracellular space into bone or soft tissue. Inadequate intestinal absorption is rare because antacids containing aluminum hydroxide are no longer commonly prescribed. Malnutrition from fasting or starvation may result in depletion of phosphate. This is also commonly seen in alcoholism. In hospitalized patients, redistribution is the main cause. Insulin promotes phosphate entry into cells along with glucose. When nutrition is initiated, refeeding further increases redistribution of phosphate into cells and is more pronounced when IV glucose is used alone.

Sepsis may cause destruction of cells and metabolic acidosis, resulting in a net shift of phosphate from the extracellular space into cells. Renal failure is associated with hyperphosphatemia, not hypophosphatemia, and initial prerenal azotemia, such as in this presentation, can obscure underlying phosphate depletion. The approach to treating hypophosphatemia should take into account several factors, including the likelihood (and magnitude) of underlying phosphate depletion, renal function, serum calcium levels, and the concurrent administration of parenteral glucose. In addition, the treating physician should assess the patient for complications of hypophosphatemia, which can include neuromuscular weakness, cardiac dysfunction, hemolysis, and platelet dysfunction. Severe hypophosphatemia generally occurs when the serum concentration falls below 2 mg/dL (<0.75 mmol/L). This becomes particularly dangerous when there is underlying chronic phosphate depletion. However, there is no simple formula to determine the body's phosphate needs from measurement of the serum phosphate levels because most phosphate is intracellular. It is generally recommended to use oral phosphate repletion when the serum phosphate levels are greater than 1.5–2.5 mg/dL (0.5–0.8 mmol/L). The dose of oral phosphate is 750–2000 mg daily of elemental phosphate given in divided doses. More severe hypophosphatemia, as in the case presented, requires IV repletion. IV phosphate repletion is given as neutral mixtures of sodium and potassium phosphate salts at doses of 0.2–0.8 mmol/kg given over 6 hours.

Table IX-96 outlines the total dose and recommended infusion rates for a range of phosphate levels. In this patient with a level of 1.0 mg/dL, the recommended infusion rate is 8 mmol/h over 6 hours for a total dose of 48 mmol. Until the underlying hypophosphatemia is corrected, one should measure phosphate and calcium levels every 6 hours. The infusion should be stopped if the calcium phosphate product rises to higher than 50 to decrease the risk of heterotopic calcification. Alternatively, if hypocalcemia is present coincident with the hypophosphatemia, it is important to correct the calcium prior to administering phosphate.

IX-97. **The answer is B.** *(Chap. 402)* Vitamin D deficiency is highly prevalent in the United States and is most common in older individuals who are hospitalized or institutionalized. Vitamin D deficiency can occur as a result of inadequate dietary intake, decreased production in the skin, decreased intestinal absorption, accelerated losses, or impaired vitamin D

TABLE IX-96 **Intravenous Therapy for Hypophosphatemia**

Consider			
Likely severity of underlying phosphate depletion			
Concurrent parenteral glucose administration			
Presence of neuromuscular, cardiopulmonary, or hematologic complications of hypophosphatemia			
Renal function (reduce dose by 50% if serum creatinine >220 μmol/L [>2.5 mg/dL])			
Serum calcium level (correct hypocalcemia first; reduce dose by 50% in hypercalcemia)			
Guidelines			
Serum Phosphorus (mM; mg/dL)	Rate of Infusion (mmol/h)	Duration (h)	Total Administered (mmol)
<0.8 (<2.5)	2	6	12
<0.5 (<1.5)	4	6	24
<0.3 (<1)	8	6	48

Rates shown are calculated for a 70-kg person; levels of serum calcium and phosphorus must be measured every 6–12 h during therapy; infusions can be repeated to achieve stable serum phosphorus levels >0.8 mmol/L (>2.5 mg/dL); most formulations available in the United States provide 3 mmol/mL of sodium or potassium phosphate.

activation in the liver or kidney. Clinically, vitamin D deficiency in older individuals is most often silent. Often practitioners fail to consider vitamin D deficiency until a patient has been diagnosed with osteoporosis or suffered a fracture. However, some individuals can experience diffuse muscle and bone pain. When assessing vitamin D levels, the appropriate test is 25-hydroxyvitamin D (25[OH]D) levels. The Institute of Medicine has defined vitamin D sufficiency as a level of 25(OH)D >50 nmol/L (>20 ng/L). However, in the elderly and in some disease states, higher levels may be required to maximize intestinal calcium absorption. Levels less than 37 nmol/L (15 ng/mL) are associated with a rise in parathyroid hormone (PTH) levels and a fall in bone density. Vitamin D deficiency may also lead to decreased intestinal absorption of calcium with resultant hypocalcemia and secondary hyperparathyroidism. As a result, there is higher bone turnover, which can be associated with an increase in alkaline phosphatase levels. In addition, elevated PTH stimulates renal conversion of 25(OH)D to 1,25-hydroxyvitamin D (1,25[OH]D), the activated form of vitamin D. Thus, even in the face of severe vitamin D deficiency, the activated 1,25(OH)D levels may be normal and do not accurately reflect vitamin D stores. Thus, 1,25(OH)D should not be used to make a diagnosis of vitamin D deficiency. Although vitamin D deficiency may be associated with abnormalities in PTH, alkaline phosphatase, and calcium levels, these biochemical abnormalities are seen in many other diseases and are neither sensitive nor specific for the diagnosis of vitamin D deficiency.

IX-98. **The answer is D.** *(Chap. 402)* Vitamin D deficiency is common in all areas of the United States and has resulted from decreased solar exposure with deficient production of vitamin D in the skin, lack of dietary intake, accelerated losses of vitamin D, impaired vitamin D activation, or resistance to the biologic effects of 1,25(OH)2D, the activated form of vitamin D. Vitamin D stores are best assessed by measuring 25(OH)D. Levels less than 20 ng/L (<50 nmol/L) should be repleted. The recommended daily intake in the absence of vitamin D deficiency is 800 IU of vitamin D, typically administered as vitamin D_3 or cholecalciferol, daily. However, higher doses of vitamin D are required when vitamin D deficiency is present to return vitamin D levels to normal. In most individuals, supplementation with vitamin D_3 at 2000 IU daily along with calcium supplementation would be recommended. In severe cases of vitamin D deficiency, high-dose repletion may be required. This is given as ergocalciferol (vitamin D) 50,000 IU weekly for 3 to 12 weeks before decreasing to the maintenance daily dose of cholecalciferol 800 IU daily.

IX-99. **The answer is E.** *(Chap. 404)* There is no established algorithm for the evaluation of women who present with osteoporosis. A general evaluation that includes complete blood count, serum and 24-hour urine calcium, and renal and hepatic function tests is useful for identifying selected secondary causes of low bone mass, particularly for women with fractures or unexpectedly low Z-scores. An elevated serum calcium level suggests hyperparathyroidism or malignancy, whereas a reduced serum calcium level may reflect malnutrition or a malabsorption disease such as celiac disease. In the presence of hypercalcemia, a serum parathyroid hormone (PTH) level differentiates between hyperparathyroidism (PTH↑) and malignancy (PTH↓), and a high parathyroid hormone-related peptide level can help document the presence of humoral hypercalcemia of malignancy. A low urine calcium (<50 mg/24 h) suggests malnutrition, or malabsorption; a high urine calcium (>300 mg/24 h) during normal calcium intake (excluding calcium supplements for at least a week before the urine collection) is indicative of hypercalciuria. Hypercalciuria occurs primarily in three situations: (1) a renal calcium leak, which is more common in males with osteoporosis; (2) absorptive hypercalciuria, which can be idiopathic or associated with increased 1,25$(OH)_2$D in granulomatous disease; or (3) hematologic malignancies or conditions associated with excessive bone turnover such as Paget disease, hyperparathyroidism, and hyperthyroidism. Individuals who have osteoporosis-related fractures or bone density in the osteoporotic range should have a measurement of serum 25(OH)D level, since the intake of vitamin D required to achieve a target level >30 ng/mL is highly variable. Hyperthyroidism should be evaluated by measuring thyroid-stimulating hormone (TSH). An increased TSH is consistent with hypothyroidism rather than hyperthyroidism. When there is clinical suspicion of Cushing syndrome, urinary free cortisol levels or a fasting serum cortisol should be measured after overnight dexamethasone. A decreased morning cortisol is suggestive of adrenal insufficiency rather than Cushing syndrome. When bowel disease, malabsorption, or malnutrition is suspected, serum albumin, cholesterol, and a complete blood count should be checked. Asymptomatic malabsorption may be heralded by anemia (macrocytic—vitamin B_{12} or folate deficiency; microcytic—iron deficiency) or low serum cholesterol or urinary calcium levels. If these or other features suggest malabsorption, further evaluation is required. Asymptomatic celiac disease with selective malabsorption is being found with increasing frequency; the diagnosis can be made by testing for transglutaminase IgA antibodies, but it may require confirmation by endoscopic biopsy. A trial of a gluten-free diet can also be confirmatory.

IX-100. The answer is C. *(Chap. 404)* A large body of data indicates that optimal calcium intake reduces bone loss and suppresses bone turnover. Recommended intakes from an Institute of Medicine (IOM) report are shown in Table IX-100. The National Health and Nutritional Evaluation Survey (NHANES) have consistently documented that average calcium intakes fall considerably short of these recommendations. The preferred source of calcium is diet, but many patients require calcium supplementation to bring intake to about 1200 mg/d. Best sources of calcium include dairy products (milk, yogurt, and cheese), nondairy milks (almond, rice, soy), and fortified foods such as certain cereals, waffles, snacks, juices, and crackers. Diet alone rarely contains sufficient vitamin D to maintain target circulating levels (serum 25[OH]D consistently >75 μmol/L [30 ng/mL]). Vitamin D is synthesized from a precursor in the skin under the influence of heat and ultraviolet light, but production is blocked by sunscreen and sun avoidance. Therefore, large segments of the population do not obtain sufficient vitamin D from either skin production or dietary sources.

TABLE IX-100 Adequate Calcium Intake

Life Stage Group	Estimated Adequate Daily Calcium Intake (mg/d)
Young children (1–3 years)	500
Older children (4–8 years)	800
Adolescents and young adults (9–18 years)	1300
Men and women (19–50 years)	1000
Men and women (51 and older)	1200

Note: Pregnancy and lactation needs are the same as for nonpregnant women (e.g., 1300 mg/d for adolescents/young adults and 1000 mg/d for ≥19 years).
Source: Data from the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Food and Nutrition Board. Institute of Medicine. Washington: National Academy Press, 1997.

Since vitamin D supplementation at doses that would achieve these serum levels is safe and inexpensive, the National Academy of Medicine (formerly, IOM) recommends daily intakes of 200 IU for adults <50 years of age, 400 IU for those 50–70 years, and 600 IU for those >70 years (based on obtaining a serum level of 20 ng/mL, lower than the level recommended by most other guidelines). Multivitamin tablets usually contain 400 IU, and many calcium supplements also contain vitamin D. Some data suggest that higher doses (≥1000 IU) may be required in the elderly and chronically ill. The IOM report suggests that it is safe to take up to 4000 IU/d. For those with osteoporosis or those at risk of osteoporosis 1000–2000 IU/day can usually maintain serum 25(OH)D above 30 ng/mL.

IX-101. The answer is B. *(Chap. 404)* Osteoporosis refers to a chronic condition characterized by decreased bone strength and frequently manifests as vertebral and hip fractures. In the United States, about 8 million women have osteoporosis compared with about 2 million men, for a ratio in women to men of 4 to 1. An additional 48 million individuals are estimated to have osteopenia. The risk of osteoporosis increases with advancing age and rapidly worsens following menopause in women. Most women meet the diagnostic criteria for osteoporosis between the ages of 70 and 80. White women have an increased risk for osteoporosis when compared with African American women. The epidemiology for bone fractures follows the epidemiology for osteoporosis. Fractures of the distal radius (Colles fracture) increase up to age 50 and plateau by age 60, and there is only a modest increase in risk thereafter. This is contrasted with the risk of hip fractures. Incidence rates for hip fractures double every 5 years after the age of 70. This change in fracture pattern is not entirely due to osteoporosis but is also related to the fact that fewer falls in the elderly occur onto an outstretched arm and are more likely to occur directly on the hip. Black women experience hip fractures at approximately half the rate as white women. The mortality rate in the year following a hip fracture is 5–20%. Vertebral fractures are also common manifestations of osteoporosis. Although most are found incidentally on chest radiograph, severe cases can lead to height loss, pulmonary restriction, and respiratory morbidity.

IX-102. The answer is C. *(Chap. 404)* There are multiple risks for osteoporotic bone fractures that can be either modifiable or nonmodifiable (Table IX-102). Nonmodifiable risk factors include a previous history of fracture as an adult, female sex, white race, dementia, advanced age, and history of fracture (but not osteoporosis) in a first-degree relative. Risk factors that are potentially modifiable include low calcium intake, alcoholism, impaired eyesight, recurrent falls, inadequate physical activity, poor health, and estrogen deficiency, including menopause prior to age 45 or prolonged premenstrual amenorrhea. Excessive thinness and low body weight are also risk factors for osteoporosis, although the osteoporosis guidelines do not clearly delineate what is considered excessive thinness. Current cigarette smoking is a risk factor for osteoporosis-related fracture, whereas a prior history of cigarette use is not. This patient has already modified her risk by quitting smoking.

TABLE IX-102 Risk Factors for Osteoporosis Fracture

Nonmodifiable	Potentially Modifiable
Personal history of fracture as an adult	Current cigarette smoking
History of fracture in first-degree relative	Estrogen deficiency
Female gender	Early menopause (<45 years) or bilateral ovariectomy
Advanced age	Prolonged premenstrual amenorrhea (>1 year)
White race	Poor nutrition especially low calcium and vitamin D intake
Dementia	Alcoholism
	Impaired eyesight despite adequate correction
	Recurrent falls
	Inadequate physical activity
	Poor health/frailty

IX-103. The answer is C. *(Chap. 404)* Determination of when to initiate screening for osteoporosis with bone densitometry testing can be complicated by multiple factors. In general, most women do not require screening for osteoporosis until after completion of menopause unless there have been unexplained fractures or other risk factors that would suggest osteoporosis. There is no benefit to initiating screening for osteoporosis in the perimenopausal period. Indeed, most expert recommendations do not recommend routine screening for osteoporosis until age 65 or older unless risk factors are present. Risk factors for osteoporosis include advanced age, current cigarette smoking, low body weight (<57.7 kg), family history of hip fracture, and long-term glucocorticoid use. Inhaled glucocorticoids may cause increased loss of bone density, but because this patient is on a low dose of inhaled fluticasone and is not estrogen deficient, bone mineral densitometry cannot be recommended at this time. The risk of osteoporosis related to inhaled glucocorticoids is not well defined, but most studies suggest that the risk is relatively low. Delaying childbearing until the fourth and fifth decades does increase the risk of osteoporosis but does not cause early onset of osteoporosis prior to completion of menopause. The patient's family history of osteoporosis likewise is not an indication for early screening for osteoporosis.

IX-104 to IX-108. The answers are B, E, D, A, and C, respectively. *(Chap. 404)* In the last 20 years, multiple pharmacologic options have become available for the treatment of osteoporosis. Prior to the 1990s, estrogen, either alone or in combination with a progestin, was the primary treatment for osteoporosis. Since that time, many new agents have been introduced, although estrogen is effective at preventing bone loss and reducing bone turnover and yields small increases in bone mass of the spine, hip, and total body. The selective estrogen receptor modulator (SERM) raloxifene binds to the estrogen receptor and is approved for the prevention and treatment of osteoporosis as well as the prevention of breast cancer. Tamoxifen is another well-known SERM, but it is only approved for the treatment and prevention of breast cancer. Both drugs have a favorable effect on bone turnover and bone mass. Raloxifene has been demonstrated in clinical trials to reduce the occurrence of vertebral fracture by 30–50%, although the effect on nonvertebral fracture is not known. Bisphosphonates are the most widely used category of medications for the prevention and treatment of osteoporosis. Alendronate, risedronate, ibandronate, and zoledronic acid are approved medications in this class. Bisphosphonates act to impair osteoclast function and reduce osteoclast number by inducing apoptosis. Zoledronic acid is retained in the bone for a very long time and is dosed intravenously only once yearly. Exogenous administration of calcitonin, a polypeptide hormone produced by the thyroid gland, is sometimes administered as a nasal spray in the treatment of osteoporosis. It acts to suppress osteoclast activity by direct action on the osteoclast calcitonin receptor. In clinical studies, the effect on bone mass and vertebral fracture risk was small, and there was no effect on nonvertebral fractures. Denosumab is a fully human monoclonal antibody to RANKL, the final common effector of osteoclast formation, activity, and survival. When denosumab binds to RANKL, osteoclast maturation is significantly impaired. It is administered by subcutaneous injection twice yearly and has been demonstrated to decrease fracture risk in the spine, hip, and forearm over a 3-year period by 20–70%. Teriparatide is a recombinant parathyroid hormone (1-34hPTH) that is approved for the treatment of osteoporosis. It is administered by daily subcutaneous injection and has been shown to decrease both vertebral and nonvertebral fracture risk. Because teriparatide is an analogue of PTH, the drug acts like PTH with direct actions on osteoblast to stimulate new bone formation, which is unique among the treatments for osteoporosis.

IX-109. The answer is C. *(Chap. 405)* The radiograph demonstrates that the right femur has coarsening of the trabecular pattern with marked cortical thickening and narrowing of the joint space consistent with osteoarthritis secondary to pagetic deformity. Paget disease is a localized bone-remodeling disorder that affects widespread, noncontiguous areas of the skeleton. The pathologic process is initiated by overactive osteoclastic bone resorption followed by a compensatory increase in osteoblastic new bone formation, resulting in a structurally disorganized mosaic of woven and lamellar bone. Pagetic bone is expanded, less compact, and more vascular; thus, it is more susceptible to deformities and fractures. Although most patients are asymptomatic, symptoms resulting directly from bony involvement (bone pain, secondary arthritis, fractures) or secondarily from the expansion of bone causing compression of surrounding neural tissue are not uncommon. The most common presenting symptom of Paget disease is pain, which may result from increased bony vascularity, expanding lytic lesions, fractures, bowing, or other deformities. Bowing of the femur or tibia causes gait abnormalities and abnormal mechanical stresses with secondary osteoarthritis of the hip or knee joints. Long bone bowing also causes extremity pain by stretching the muscles attached to the bone softened by the pagetic process. Back pain results from enlarged pagetic vertebrae, vertebral compression fractures, spinal stenosis, degenerative changes of the joints, and altered body mechanics with kyphosis and forward tilt of the upper back. Paget disease is usually diagnosed from radiologic and biochemical abnormalities. Radiographic findings typical of Paget disease include enlargement or expansion of an entire bone or area of a long bone, cortical thickening, coarsening of trabecular markings, and typical lytic and sclerotic changes. Though fractures can occur as a result of Paget disease, none is present in the radiograph. Trochanteric bursitis typically causes lateral hip pain and rarely is associated with abnormalities on radiographs.

IX-110. The answer is C. *(Chap. 406)* Several types of Ehlers-Danlos syndrome (EDS) have been defined, based on the extent to which the skin, joints, and other tissues are involved; mode of inheritance; and by molecular and biochemical analysis (Table IX-110). Classical EDS includes a severe form of the disease (type I) and a milder form (type II), both characterized by joint hypermobility and skin that is velvety in texture, hyper-extensible, and easily scarred. In hypermobile EDS (type III), joint hypermobility is more prominent than skin changes. In vascular-type EDS (type IV), the skin changes are more prominent than joint changes, and the patients are predisposed to sudden death from rupture of large blood vessels or other hollow organs. EDS V is similar to EDS II but is inherited as an X-linked trait. The ocular-scoliotic type of EDS (type VI) is characterized by scoliosis, ocular fragility, and a cone-shaped deformity of the cornea (keratoconus). The arthrochalasic type of EDS (types VII A and B) is characterized by marked joint hypermobility that is difficult to distinguish from EDS III except by the specific molecular defects in the processing of type I procollagen to collagen. The periodontic-type EDS (type VIII) is distinguished by prominent periodontal changes. EDS IX–XI were defined on the basis of preliminary biochemical and clinical data. EDS due to tenascin X deficiency has not been assigned a type; it is an autosomal recessive form of the syndrome similar to EDS II. The cardiac valvular form of EDS has similar features to EDS II, but also involves severe changes to the aorta. The progeroid form of EDS displays features of both EDS and progeria. Because of overlapping signs and symptoms, many patients and families with some of the features of EDS cannot be assigned to any of the defined types. Lens dislocation is common in Marfan syndrome, not EDS, which typically results from mutations in fibrillin-1.

IX-111. The answer is A. *(Chap. 406)* Osteogenesis imperfecta (OI) is a heritable disorder of connective tissue in which there is a severe decrease of bone mass that makes bone brittle and prone to fracture due to a deficiency or abnormality in type I procollagen. The disease is often inherited in an autosomal dominant fashion. There are several subtypes of OI that are currently based on the clinical phenotype of the disease. There is debate about whether the disease should be reclassified based on genetic abnormalities, but at present, the classification based on clinical presentation remains the standard. Type 1 OI has a varied clinical presentation, but generally has the mildest bone disease with minimal or no apparent skeletal deformities. The disease may not present until adulthood in those with type 1 OI. However, type 2 OI produces very brittle bones and typically is lethal in utero or shortly after birth. Other types of OI have variable bone disease that can yield bone deformity with frequent fractures or kyphoscoliosis or result in only mild disease. Another common clinical feature of type 1 OI includes blue sclera, which is thought to be due to the thinness of the collagen fibers of the sclerae, allowing the choroid layers to be seen. Additionally, the teeth may have an amber or yellowish brown color due to a deficiency of dentin that is rich in type I collagen. The deciduous teeth are often smaller than normal, whereas the permanent teeth may be bell-shaped and restricted at the base. Hearing loss is common beginning in the second decade of life and affects >50% of individuals over the age of 30. Fractures tend to decrease after puberty in both sexes but may increase in women at the time of pregnancy and after menopause. Diagnosis of OI is usually based

TABLE IX-110 Different Forms of Ehlers-Danlos Syndrome (EDS)

Type	Typical Features	Inheritance	Gene Defect	Protein Defect
Classic (EDS I—severe and EDS II—mild)	Skin hyperextensibility and fragility, joint hypermobility, tissue fragility manifested by widened atrophic scarring	AD	*COL5A1* *COL5A2*	Collagen V
		AD	*COL1A1*	Proα1 (I) and proα2 (I) chains of procollagen I
		AD, AR	*COL1A2*	
Hypermobile (EDS III)	Joint hypermobility, moderate skin involvement, absence of tissue fragility	AD	*TNXB*	Tenascin X
Vascular (EDS IV)	Markedly reduced life span due to spontaneous rupture of internal organs such as arteries and intestines; skin is thin, translucent, and fragile, with extensive bruising; hypermobile minor joints; characteristic facial appearance	AD	*COL3A1*	Collagen III
Ocular-scoliotic EDS VI (EDS VIA and EDS VIB)	Features of classic EDS as well as severe muscular hypotonia after birth, progressive kyphoscoliosis, a marfanoid habitus, osteopenia, occasionally rupture of the eye globe and great arteries	AR	*PLOD1*	Deficiency of procollagen-lysine 5-dioxygenase activity (EDS VIA)
			Unknown for EDS VIB	Unknown for EDS VIB
Arthrochalasic EDS VII (EDS VIIA and EDS VIIB)	Congenital bilateral hip dislocation, hypermobile joints, moderate skin involvement, osteopenia	AD	*COL1A1* *COL1A2*	Mutations that prevent cleavage of the N propeptides
Dermatosparactic EDS VIIC	Redundant and fragile skin, prominent hernias, joint laxity, dysmorphic features	AR	*ADAMTS2*	Deficiency of procollagen I N-terminal proteinase
Periodontic EDS VIII	Absorptive periodontosis with premature loss of permanent teeth, fragility of the skin, skin lesions	AD	C1R C1S	Components of the complement pathway
EDS due to tenascin X deficiency	Similar to EDS II	AR	*TNXB*	Tenascin X
EDS, cardiac valvular form	Similar to EDS II	AR	*COL1A2*	Type I collagen deficiency
EDS, progeroid form	Similar to EDS I–III with hair loss, hypotonia, and aged appearance	AR	*B4GALT7*	Deficiency of galactosyltransferase 7 (defective synthesis of dermatan sulfate proteoglycans)
EDS, musculocontractural form	Hyperextensible and thin skin, hypermobility and contractures of hands and feet, kyphoscoliosis	AR	*CHST14* *DSE*	Dermatan 4-*O*-sulfotransferase 1 (*CHST14*) and DS epimerase 1 (*DSE*) leading to defective synthesis of dermatan sulfate proteoglycans

Abbreviations: AD, autosomal dominant; AR, autosomal recessive.

on clinical criteria in an individual with fractures and other typical clinical features. Given the autosomal dominant nature of inheritance, a family history of disease may be present. Decreased bone mineral density is demonstrated in a variety of imaging techniques including x-ray absorptiometry and plain radiographs. Bone biopsy is not required for diagnosis and may cause morbidity. Treatment of the disease is primarily aimed at treating complications.

Fractures typically are only slightly displaced with little soft tissue swelling. Fragile blood vessels may also be present which causes easy bruising. Minimal support and traction are required. Although bisphosphonates are well tolerated and often used for moderate to severe disease, where they may decrease bony pain and fracture risk, their long-term effects and safety in osteogenesis imperfecta are unknown.

IX-112. The answer is A. *(Chap. 406, http://www.marfan.org/dx/home)* This patient presents with evidence of Marfan syndrome (MFS), an autosomal disorder most commonly associated with mutations in the fibrillin-1 gene. MFS is one of the most common heritable connective tissue disorders, with an incidence of 1 in 3000–5000 and is found in most racial and ethnic groups. The diagnosis of MFS is based on the revised Ghent criteria, which include major and minor criteria for evaluation. In the most recent revision, there has been stronger emphasis on the cardiovascular and ocular manifestations of MFS. In the absence of family history, the presence of aortic root aneurysm and ectopia lentis is sufficient to make the diagnosis. The diagnosis can also be made with a combination of systemic manifestations and the presence of aortic root dilation or ectopia lentis. Some of the systemic manifestations that this patient exhibits include the presence of long limbs and tall stature.

The ratio of the upper segment to the lower segment of the body is usually 2 standard deviations below mean for age, race, and sex, and the arm span is usually >1.05 times the height. Arachnodactyly with long, slender fingers and hands is present. Other skeletal deformities include pectus excavatum, pectus carinatum, scoliosis, kyphosis, pes planus, and high arched palate. A calculator is available at http://www.marfan.org/dx/score to allow one to easily calculate the number of systemic symptoms an individual has on presentation. In individuals with a family history of MFS, the presence of ectopia lentis, aortic root dilation, or a positive systemic score would be adequate for diagnosis. In this clinical scenario, the patient has a strong likelihood of having MFS and should be advised to refrain from engaging in strenuous physical activity or contact sports immediately, although further workup with echocardiogram and slit-lamp examination will be required. Although there is no definitive family diagnosis, the sudden death of the patient's father is likely to represent an aortic aneurysm rupture. In the most recent diagnostic criteria, an echocardiogram would be required for definitive diagnosis to evaluate for aortic root dilation. However, because this patient has several clinical features and a murmur concerning for aortic regurgitation, an echocardiogram would not be required before acting in the best interest of the man's health and removing him from further physical activity. Cardiovascular abnormalities may include mitral valve prolapse with or without mitral regurgitation and aortic root dilation. Dilation of the aortic root and the sinuses of Valsalva are characteristic of MFS and are an ominous sign of the disease. The dilation can occur at any age and place the patient at risk for aortic regurgitation, aortic dissection, and aneurysmal rupture. Dilation can be accelerated by physical and emotional stress and pregnancy. Individuals may require surgical repair of the dilated aortic root, and routine follow-up echocardiography is required to ensure that further dilation is not occurring. Use of beta blockers and, more recently, angiotensin II receptor blockers has been demonstrated to reduce the rate or delay the onset of aortic dilation. Physical activity guidelines have been published that suggest that all patients with MFS should avoid strenuous physical activity and contact sports. However, regular exercise that is low impact and low intensity should be encouraged.

IX-113. The answer is D. *(Chap. 407)* The therapy of hemochromatosis involves removal of the excess body iron and supportive treatment of damaged organs. Iron removal is best accomplished by weekly or twice-weekly phlebotomy of 500 mL. Although there is an initial modest decline in the volume of packed red blood cells to about 35 mL/dL, the level stabilizes after several weeks. The plasma transferrin saturation remains increased until the available iron stores are depleted. In contrast, the plasma ferritin concentration falls progressively, reflecting the gradual decrease in body-iron stores. One 500-mL unit of blood contains 200–250 mg of iron, and ≥25 g of iron may have to be removed. Therefore, in patients with advanced disease, weekly phlebotomy may be required for 1–2 years, and it should be continued until the serum ferritin level is ≤100 μg/L. Thereafter, phlebotomies are performed at appropriate intervals to maintain ferritin levels at ≤100 μg/L. The transferrin saturation fluctuates and may still be elevated but should not dictate further therapy unless it is persistently at 100% when free unbound iron may circulate. Usually one phlebotomy every 3 months will suffice. It is important, however, not to overtreat and render the patient iron deficient. Chelating agents such as deferoxamine, when given parenterally, remove 10–20 mg of iron per day, which is much less than that mobilized by once-weekly phlebotomy. Phlebotomy is also less expensive, more convenient, and safer for most patients. An effective oral iron chelating agent, deferasirox (Exjade), is now available. Alcohol consumption should be severely curtailed or eliminated because it increases the risk of cirrhosis in hereditary hemochromatosis nearly 10-fold. Dietary adjustments are unnecessary, although vitamin C and iron supplements should be avoided. The management of hepatic failure, cardiac failure, and diabetes mellitus is similar to conventional therapy for these conditions. Loss of libido and change in secondary sex characteristics are managed with testosterone replacement or gonadotropin therapy. End-stage liver disease may be an indication for liver transplantation, although results are improved if the excess iron can be removed beforehand.

IX-114. The answer is E. *(Chap. 407)* Hereditary hemochromatosis is a common genetic condition. One of 10 individuals of northern European ancestry will be a heterozygous carrier for the most common mutation, HFE, and 0.3–0.5% of the population are homozygous for this mutation. However, disease expression in individuals who are homozygous for the HFE gene varies widely and is modified by a variety of environmental and clinical factors including alcohol intake, dietary iron intake, blood loss from pregnancy and menstruation, and blood donation. It is estimated that about 30% of men who are homozygous for the HFE gene will develop symptomatic iron overload, with about 6% progressing to hepatic cirrhosis. In women, clinical disease is less prevalent, with only 1% progressing to cirrhosis. Clinical manifestations include iron overload (as measured biochemically) initially without symptoms, and then iron overload with symptoms. Initial symptoms often include lethargy, arthralgia, change in skin color, loss of libido, and diabetes mellitus. Cirrhosis, cardiac arrhythmias, and infiltrative cardiomyopathy are later manifestations. Because the clinical manifestations of the disease can be prevented with iron chelation and the mutation is so common, some have advocated for screening the population for evidence of iron overload.

Although routine screening remains controversial, recent studies indicate that it is highly effective for primary care physicians to screen subjects using transferrin saturation and serum ferritin levels. This will detect anemia and iron deficiency as well. Liver biopsy or MRI may demonstrate later findings of increased iron deposition and/or cirrhosis, but these are more costly, possibly invasive, or risky and not recommended for screening. Genetic testing is also not recommended as a first step, although it is indicated if evidence of iron overload is found on serum iron studies. No HFE activity assay is currently available.

IX-115. The answer is E. *(Chap. 407)* This patient presents with the classic finding of diffuse organ iron infiltration due to hemochromatosis. The iron accumulation in the pancreas, testes, liver, joints, and skin explains his findings. Hemochromatosis is a common disorder of iron storage in which inappropriate increases in intestinal iron absorption result in excessive deposition in multiple organs, but predominantly in the liver. There are two forms: hereditary hemochromatosis, in which the majority of cases are associated with mutations of the HFE gene, and secondary iron overload, which usually is associated with iron-loading anemias such as thalassemia and sideroblastic anemia. In this case, without a history of prior hematologic disease, the most likely diagnosis is hereditary hemochromatosis.

Serum ferritin testing and plasma iron studies can be very suggestive of the diagnosis, with the ferritin often >500 μg/L and transferrin saturation of 50–100%. However, these tests are not conclusive, and further testing is still required for the diagnosis. Although liver biopsy and evaluation for iron deposition or a hepatic iron index ([μg/g dry weight]/56 Å ~ age >2) provide the definitive diagnosis, genetic testing is widely available today and is recommended for diagnostic evaluation because of the high prevalence of HFE gene mutations associated with hereditary hemochromatosis. If the genetic testing is inconclusive, an invasive liver biopsy evaluation may be indicated. Anti–smooth muscle antibody testing is useful for the evaluation of autoimmune hepatitis and is indicated in any case of cryptogenic cirrhosis. Plasma ceruloplasmin is the initial study in the evaluation of Wilson disease, which is also a cause of occult liver disease. However, Wilson disease would not be likely to be associated with pancreatic, joint, and skin findings. If chronic hepatitis B is suspected, a viral load or surface antigen test would be indicated. Hepatitis B surface antibody is useful to demonstrate resolved hepatitis B or prior vaccination. Hepatic ultrasound is useful in the evaluation of acute and chronic liver disease to demonstrate portal flow or vascular occlusion; it may be useful in the physiologic evaluation of this patient but would have little diagnostic value.

IX-116. The answer is E. *(Chap. 408)* In Wilson disease when severe hepatic failure occurs, hemolytic anemia may develop because large amounts of copper derived from hepatocellular necrosis are released into the bloodstream. The neurologic manifestations of Wilson disease typically occur in patients in their early 20s, although the age of onset extends into the sixth decade of life. MRI and CT scans reveal damage in the basal ganglia and occasionally in the pons, medulla, thalamus, cerebellum, and subcortical areas. The three main movement disorders include dystonia, incoordination, and tremor. Dysarthria and dysphagia are common. In some patients, the clinical picture closely resembles that of Parkinson disease. Dystonia can involve any part of the body and eventually leads to grotesque positions of the limbs, neck, and trunk. Autonomic disturbances may include orthostatic hypotension and sweating abnormalities as well as bowel, bladder, and sexual dysfunction. Memory loss, migraine-type headaches, and seizures may occur. Patients have difficulty focusing on tasks, but cognition usually is not grossly impaired. Sensory abnormalities and muscular weakness are not features of the disease. Half of patients with neurologic disease have a history of behavioral disturbances with onset in the 5 years before diagnosis. The features are diverse and may include loss of emotional control (temper tantrums, crying bouts), depression, hyperactivity, or loss of sexual inhibition. Some female patients have repeated spontaneous abortions, and most become amenorrheic prior to diagnosis. Cholelithiasis and nephrolithiasis occur with increased frequency. Some patients have osteoarthritis, particularly of the knee. Microscopic hematuria is common, and levels of urinary excretion of phosphates, amino acids, glucose, or urates may increase; however, a full-blown Fanconi syndrome is rare. Sunflower cataracts and Kayser-Fleischer rings (*copper* deposits in the outer rim of the cornea) may be seen. Electrocardiographic and other cardiac abnormalities have been reported but are not common.

IX-117. and IX-118. The answers are E and D, respectively. *(Chap. 408)* This patient presents with liver disease, hemolysis, and psychiatric illness, which suggests the presence of Wilson disease. Wilson disease is an autosomal recessive disorder caused by mutations in the ATP7B gene, a copper-transporting ATPase. As a result of this mutation, patients store abnormally high levels of copper in their liver initially, but later, copper is stored in other organs such as the brain. Although liver dysfunction is a hallmark of the disease, it may have several presentations, such as acute hepatitis, cirrhosis, or hepatic decompensation, as in this patient. Hemolysis may complicate acute decompensation because of massive release of copper from the liver into the blood, leading to hemolysis. Accumulation of copper in the basal ganglia results in Parkinson-like syndromes. Up to 50% of patients with Wilson disease will have Kayser-Fleischer rings on ocular slit-lamp examination. These brownish rings surrounding the cornea are due to copper deposition within the cornea and are diagnostic when found. Twenty-four-hour urinary copper levels are universally elevated in this disease and are the primary diagnostic modality when Kayser-Fleischer rings are absent.

Liver biopsy can also be used to confirm increased copper content. Although MRI will show basal ganglia damage, it is not specific for Wilson disease. HFE mutation is present in hemochromatosis, which this patient does not have. Urine iron levels are not indicated.

Therapy for Wilson disease is dependent on the degree of disease at the time of presentation. Patients with mild hepatitis may be treated with zinc, which blocks intestinal absorption of copper, results in a negative copper balance, and induces hepatic metallothionein synthesis, which sequesters additional toxic copper. Trientine serves as a copper chelator and is used for more severe liver dysfunction or neurologic or psychiatric disease. In acutely decompensated liver failure, zinc should not be administered for at least 1 hour following trientine because the zinc could be chelated instead of copper if administered simultaneously. Liver transplantation may be indicated in cases of fulminant hepatic failure and effectively cures the disease.

IX-119. The answer is E. *(Chap. 409)* This is a case of acute intermittent porphyria. The major manifestations of the acute hepatic porphyrias are neurologic, including neuropathic abdominal pain, peripheral motor neuropathy, and mental disturbances, with attacks often precipitated by dieting, certain porphyrinogenic drugs, and hormonal changes (Table IX-119). An acute porphyria should be suspected in patients with neurovisceral

TABLE IX-119 Human Porphyrias: Major Clinical and Laboratory Features

Porphyria	Deficient Enzyme	Inheritance	Principal Symptoms: NV or CP	Enzyme Activity % of Normal	Increased Porphyrin Precursors and/or Porphyrins		
					Erythrocytes	Urine	Stool
Hepatic Porphyrias							
5-ALA-dehydratase-deficient porphyria (ADP)	ALA-dehydratase	AR	NV	~5	Zn-Protoporphyrin	ALA, coproporphyrin III	—
Acute intermittent porphyria (AIP)	HMB-synthase	AD	NV	~50	—	ALA, PBG, uroporphyrin	—
Porphyria cutanea tarda (PCT)	URO-decarboxylase	AD	CP	~20	—	Uroporphyrin, 7-carboxylate porphyrin	Isocoproporphyrin
Hereditary coproporphyria (HCP)	COPRO-oxidase	AD	NV and CP	~50	—	ALA, PBG, coproporphyrin III	Coproporphyrin III
Variegate porphyria (VP)	PROTO-oxidase	AD	NV and CP	~50	—	ALA, PBG, coproporphyrin III	Coproporphyrin III, protoporphyrin
Erythropoietic Porphyrias							
Congenital erythropoietic porphyria (CEP)	URO-synthase	AR	CP	1–5	Uroporphyrin I Coproporphyrin I	Uroporphyrin I[a] Coproporphyrin I[a]	Coproporphyrin I
Erythropoietic protoporphyria (EPP)	Ferrochelatase	AR	CP	~20–30	Protoporphyrin	—	Protoporphyrin
X-linked protoporphyria (XLP)	ALA-synthase 2	XL	CP	>100[b]	Protoporphyrin	—	Protoporphyrin

[a] Type I isomers.

[b] Increased activity due to "gain-of-function" mutations in *ALAS2* exon 11.

Abbreviations: AD, autosomal dominant; ALA, 5-aminolevulinic acid; AR, autosomal recessive; COPRO I, coproporphyrin I; COPRO III, coproporphyrin III; CP, cutaneous photosensitivity; HMB, hydroxymethylbilane; ISOCOPRO, isocoproporphyrin; + NV, neurovisceral; PBG, porphobilinogen; PROTO, protoporphyrin IX; URO I, uroporphyrin I; URO III, uroporphyrin III; XL, X-linked.

symptoms after puberty. Symptoms include acute abdominal pain, nausea, vomiting, tachycardia, hypertension, and motor neuropathy. As these symptoms are common, other causes should be ruled out. The diagnosis is made by measuring urinary porphyrin precursors (ALA and PBG) in a spot sample of urine. Urinary PBG is always increased during acute attacks of acute intermittent porphyria and is not substantially increased in any other medical condition. Therefore, this measurement is both sensitive and specific. None of the other laboratory findings are features of acute intermittent porphyria.

IX-120. The answer is C. *(Chap. 409)* This patient has porphyria cutanea tarda (PCT), the most common of the porphyrias. Although PCT can be inherited, it most commonly occurs sporadically and is associated with a defect in hepatic uroporphyrinogen (URO) decarboxylase. For clinical symptoms to be present, the patient needs to have less than 20% of normal enzyme activity, and PCT occurs when an individual develops an inhibitor of URO decarboxylase in the liver. The majority of PCT patients have no mutations in URO decarboxylase. The major clinical feature of PCT is blistering skin lesions predominantly affecting the back of the hands that also may involve the forearms, face, legs, and feet. The lesions start as blisters that rupture and crust over, leaving scarring. Chronically, the areas most involved can develop thickened skin similar to systemic sclerosis. Precipitating factors for development of lesions include hepatitis C, HIV, excess alcohol, elevated iron levels, and estrogens. Diagnosis of PCT is made by measuring porphyrin levels, which would demonstrate elevated plasma, urine, and fecal porphyrins. Liver levels of porphyrins are also high. Urinary 5-aminolevulinic acid level may be slightly elevated, but the urinary porphobilinogen level is normal. In addition to avoiding precipitating factors, treatment of PCT is primarily through phlebotomy every 1–2 weeks to achieve a low-normal ferritin level. With this approach, a complete remission can almost always be achieved, typically after only five to six phlebotomies. After remission, continued phlebotomy may not be required, but plasma porphyrin levels should continue to be followed every 6–12 months to assess for recurrence. An alternative effective treatment is the antimalarial drugs chloroquine or hydroxychloroquine. These drugs complex with the excess porphyrins and promote their excretions. Doses typically are lower in PCT because standard doses may actually worsen symptoms transiently. Recent studies have shown that hydroxychloroquine may be as safe and effective as phlebotomy, although phlebotomy remains the standard of care at this time. None of the other treatments, including hemin, are used in the treatment of PCT.

IX-121. The answer is B. *(Chap. 411)* Gaucher disease type 1 is a non-neuronopathic disease (i.e., absence of early-onset or progressive central nervous system disease) presenting in childhood to adulthood as slowly to rapidly progressive visceral disease. About 55–60% of patients are diagnosed at <20 years of age in white populations and at even younger ages in other groups. This pattern of presentation is distinctly bimodal, with peaks at <10–15 years and at ~25 years. Younger patients tend to have greater degrees of hepatosplenomegaly and accompanying blood cytopenias. In contrast, the older patients have a greater tendency for chronic bone disease. All patients with Gaucher disease have nonuniform infiltration of bone marrow by lipid-laden macrophages termed *Gaucher cells.* This phenomenon can lead to marrow packing with subsequent infarction, ischemia, necrosis, and cortical bone destruction. Bone marrow involvement spreads from proximal to distal in the limbs and can involve the axial skeleton extensively, causing vertebral collapse. In addition to bone marrow involvement, bone remodeling is defective, with loss of total bone calcium leading to osteopenia, osteonecrosis, avascular infarction, and vertebral compression fractures with spinal cord involvement. Aseptic necrosis of the femoral head is common, as is fracture of the femoral neck. About 1 in 30 Ashkenazi Jews is a carrier for Tay-Sachs disease (total hexosaminidase A [Hex A] deficiency), resulting from defective α chains. The infantile form is a fatal neurodegenerative disease with macrocephaly, loss of motor skills, increased startle reaction, and a macular cherry red spot. The juvenile-onset form presents as ataxia and dementia, with death by age 10–15 years. Fabry disease, an X-linked disorder, results from mutations in *GALA* that encodes α-galactosidase A. The estimated prevalence of hemizygous males ranges from 1 in 40,000 to 1 in 3500 in selected populations. Clinically, the disease manifests with angiokeratomas (telangiectatic skin lesions); hypohidrosis; corneal and lenticular opacities; acroparesthesia; and progressive small-vessel disease of the kidney, heart, and brain. Cystic fibrosis typically presents with pulmonary manifestations or gastrointestinal malabsorption and is not associated with Ashkenazi Jewish ancestry. Sickle cell anemia can cause bony infarcts but is associated with a hemolytic anemia and is seen predominantly in patients of African descent.

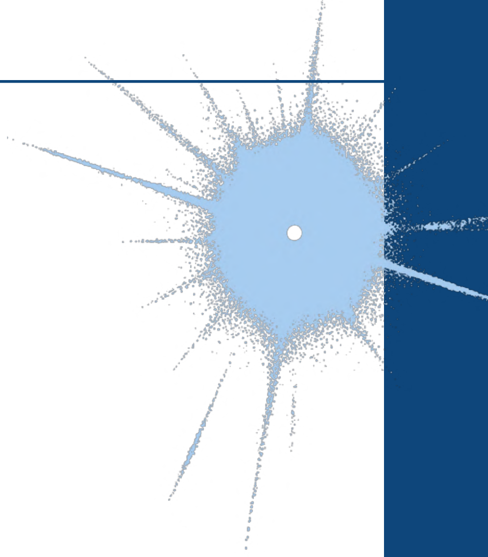
IX-122. The answer is E. *(Chap. 412)* Pompe disease is an autosomal recessive disorder caused by a deficiency of lysosomal acid α-1,4 glucosidase, an enzyme responsible for the degradation of glycogen in the lysosomes. The disorder encompasses a range of phenotypes. The most severe is the infantile form, with cardiomegaly, hypotonia, and death before 2 years of age. The late-onset form (juvenile/late-childhood or adult form [LOPD]) is characterized primarily by skeletal muscle manifestations and respiratory muscle involvement, and a more slowly progressive course. The juvenile form typically presents as delayed motor milestones (if age of onset is early enough) and difficulty in walking. Adults typically present between the second and seventh decades with slowly progressive myopathy without overt cardiac involvement. The clinical picture is dominated by slowly progressive, predominantly proximal limb girdle muscle weakness. The pelvic girdle, paraspinal muscles, and diaphragm are most seriously affected. Respiratory symptoms include somnolence, morning headache, orthopnea, and exertional dyspnea. Laboratory findings include elevated levels of serum creatine kinase (CK), aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase. Levels of urine glucose tetrasaccharide

(GlC_4), a breakdown product of glycogen, are elevated, especially on the severe end of the disease spectrum, and can be used as a biomarker to monitor disease progression and treatment responsiveness. Muscle biopsy shows vacuoles that stain positive for glycogen; the muscle acid phosphatase level is increased, presumably from a compensatory increase of lysosomal enzymes. Electromyography reveals myopathic features, with irritability of muscle fibers and pseudomyotonic discharges, which appears early in the paraspinal muscles. Serum CK is not always elevated in adults and, depending on the muscle biopsied or tested, muscle histology or electromyography may not be abnormal. Amyotrophic lateral sclerosis affects the upper and lower motor neurons and no upper motor neuron symptoms are present in this patient. Dermatomyositis has characteristic skin rashes often associated and muscle biopsy will show perifascicular atrophy and perivascular inflammation. Guillain-Barré syndrome typically has an acute onset and decreased reflexes are noted on physical examination. Chronic fatigue syndrome does not cause objective muscle weakness.

IX-123. **The answer is C.** *(Chap. 414)* Cystinuria (frequency of 1 in 10,000 to 1 in 15,000) is an autosomal recessive disorder caused by defective transporters in the apical brush border of proximal renal tubule and small intestinal cells. It is characterized by impaired reabsorption and excessive urinary excretion of the dibasic amino acids lysine, arginine, ornithine, and cystine. Because cystine is poorly soluble, its excess excretion predisposes to the formation of renal, ureteral, and bladder stones. Such stones are responsible for the signs and symptoms of the disorder. Cystine stones account for 1–2% of all urinary tract calculi but are the most common cause of stones in children. Stone formation usually manifests in the second or third decade but may occur in the first year of life. Symptoms and signs are those typical of urolithiasis: hematuria, flank pain, renal colic, obstructive uropathy, and infection. Recurrent urolithiasis may lead to progressive renal insufficiency. Cystinuria is suspected after observing typical hexagonal crystals in the sediment of acidified, concentrated, chilled urine, or after performing a urinary nitroprusside test. Quantitative urine amino acid analysis confirms the diagnosis of cystinuria by showing selective overexcretion of cystine, lysine, arginine, and ornithine. Management is aimed at preventing cystine crystal formation by increasing urinary volume and by maintaining an alkaline urine pH. Fluid ingestion in excess of 4 L/d is essential, and 5–7 L/d is optimal.

SECTION X

Neurologic Disorders



QUESTIONS

DIRECTIONS: Choose the one best response to each question.

X-1. In evaluating a patient with a new focal neurologic deficit, which of the following should be the first diagnostic priority?

- A. Obtaining an echocardiogram to evaluate for possible etiology of emboli
- B. Obtaining an electroencephalogram to rule out seizures
- C. Obtaining laboratory studies to rule out a metabolic reason for the supposed neurologic complaint
- D. Obtaining rapid MRI with and without contrast
- E. Obtaining the history and examination to identify the region of the nervous system that is likely to be responsible for the symptoms

X-2. Which of the following is usually the first to be affected (e.g., is the patient most likely to name incorrectly) in assessment of patient orientation?

- A. Location
- B. Name
- C. Time
- D. None of the above

X-3. You are evaluating a 53-year-old woman with neurologic complaints reminiscent of a demyelinating disease. Which of the following evaluative modalities is recommended for further workup of demyelinating disease?

- A. CT angiography
- B. CT
- C. Electroencephalogram
- D. MRI
- E. Transcranial Dopplers

X-4. Ms. Johann is an 84-year-old woman with well-controlled diabetes and a history of multiple myeloma who presents with acute headache and undergoes CT scan with IV contrast, which shows no acute intracranial abnormalities. While her admission creatinine was 2.1, on post-admission day 2 it is 2.6 and rises to 3.6 on the next day. She is not dehydrated, she has not received any other nephrotoxic agents, and a diagnosis of contrast-induced nephropathy is made. All of the following are risk factors for contrast-induced nephropathy EXCEPT:

- A. Age >80 years
- B. Diabetes mellitus
- C. Low-contrast dose
- D. Paraproteinemia
- E. Pre-existing renal disease

X-5. You are seeing a patient in the clinic who suffered nephrogenic systemic fibrosis (NSF) after gadolinium administration for an MRI years ago. Which of the following is the strongest risk for NSF?

- A. Advanced age
- B. Diabetes
- C. Glomerular filtration rate <30
- D. Heart failure
- E. Hypertension

X-6. You are promoted to the head of safety of the radiology department for a day while the remainder of the department is gone to a national scientific meeting. The head of maintenance approaches you to schedule floor buffing for the MRI room with a heavy, metal buffer machine, a task which he is shocked to find has not ever been performed. Your response should be:

A. "Any time!"
B. "As long as no patients are present, it should be fine."
C. "Let me first turn the magnet off."
D. "Make sure the maintenance worker holds on tight!"
E. " You cannot do that."

X-7. All of the following statements regarding astrocytes are true EXCEPT:

A. They actively phagocytose synapses.
B. They exert effects on the life of synapses through their secretory function.
C. They function only as interstitial supporting cells for neuronal migration.
D. They make up at least half of all central nervous system cells.
E. They participate in the dynamic regulation of local vascular tone.

X-8. A 45-year-old woman is admitted to the emergency room after a first episode of witnessed generalized tonic-clonic seizure. She is administered lorazepam 2 mg with cessation of seizure activity. All of the following are likely possible causes of her seizure EXCEPT:

A. Alcohol withdrawal
B. Autoantibodies
C. Brain tumor
D. Genetic disorder
E. Hyperglycemia

X-9. A 24-year-old man presents to your office requesting to be taken off of his antiepileptic drugs. He was in an automobile accident at the age of 12, resulting in significant head trauma. He was in a medically induced coma for 6 weeks and had intracranial edema with generalized tonic-clonic seizures at that time. These persisted for several years afterward. The last seizure he is aware of occurred at the age of 18 and was generalized. He continues to take valproic acid 1000 mg bid. On physical examination, he demonstrates normal cognition and affect. He has ongoing focal weakness involving his left lower extremity with spasticity. You refer him for a sleep-deprived electroencephalogram, which shows no evidence of focal abnormalities. Which of the following factors is of greatest concern regarding his risk of recurrent seizures?

A. Focal defect on neurologic examination
B. Generalized seizure disorder
C. Head trauma
D. Seizure within the last 7 years

X-10. A 38-year-old man with a history of seizure disorder presents with generalized convulsive status epilepticus. He had been having persistent seizure activity for 20 minutes when emergency medical services was activated. He was given paralytic agents in the field to allow for intubation as well as lorazepam 8 mg IV. On arrival in the emergency department 20 minutes later, the neuromuscular blockade had worn off and generalized seizure activity was again apparent. His initial temperature is 39.2°C (102.5°F) with blood pressure 182/92, heart rate 158 beats/min, respiratory rate 38 breaths/min, and SaO_2 95% on mechanical ventilation with an assist control mode with a set rate of 15, tidal volume of 420 mL, PEEP of 5 cm H_2O, and FiO_2 of 0.6. Which of the following is the next step in the management of this patient?

A. Additional dosing of neuromuscular blockers
B. Isoflurane anesthesia
C. Fosphenytoin 20 mg/kg IV
D. Pentobarbital 5 mg/kg bolus followed by an infusion at 1 mg/kg/h
E. Propofol 2 mg/kg bolus followed by an infusion at 2 mg/kg/h

X-11. You are seeing a young man with seizures. As you work to classify the type and etiology of seizure, you know all of the following statements are true, EXCEPT:

A. Focal seizures originate within networks limited to one brain region.
B. Generalized seizures arise within and rapidly engage networks distributed across both cerebral hemispheres.
C. Focal seizures are not usually associated with structural abnormalities of the brain.
D. Focal seizures can evolve into generalized seizures.
E. All of the above are true.

X-12. All of the following are usually associated with absence seizures EXCEPT:

A. Lip smacking
B. Postictal confusion
C. Provocation with hyperventilating
D. Rapid blinking
E. Small amplitude clonic movements of the hands

X-13. A 76-year-old man was seen in the emergency department for left-sided arm weakness that rapidly improved over the course of 4 hours. He has a past medical history positive for hypertension, dyslipidemia, and coronary artery disease. He previously has undergone coronary angioplasty with stenting to both his left anterior descending artery and right coronary artery on two occasions. He is currently being treated with aspirin 81 mg daily, metoprolol 100 mg bid, benazepril 20 mg daily, rosuvastatin 10 mg daily, and clopidogrel 75 mg daily. Evaluation demonstrates a 75% occlusion of the right internal carotid artery. The patient is considering whether he would like to undergo carotid endarterectomy. What information is needed for him to make an informed decision about the risks and benefits of the surgery for him?

A. Perioperative mortality rate for the surgeon performing his case
B. Perioperative stroke rate for the surgeon performing his case
C. Risk of stroke in the next 90 days
D. Risk of stroke in the next year
E. The surgeon cannot schedule his surgery for 6 weeks

X-14. Ms. Weiwadell presents to you in the emergency department with acute-onset dysarthria and confusion. You make the diagnosis of stroke clinically. What is the next appropriate step?

A. Aspirin 81 mg by mouth
B. CT of the brain
C. Heparin IV drip
D. Tissue plasminogen activator
E. None of the above

X-15. Mr. Geralt is admitted with fever, chills, and cough. He has a history of a prior left middle cerebral artery (MCA) stroke from which he suffers no day-to-day neurologic deficits. On arrival, chest x-ray demonstrates pneumonia and antibiotics are started. You are called to the bedside for neurologic changes and find that he has mild dysarthria and right-sided weakness. CT shows no infarction and CT angiography (CTA) shows no acute arterial occlusion. Which of the following explains the patient's findings?

A. Microemboli to the left MCA territory
B. New thrombotic stroke unseen by CT and CTA
C. Ongoing seizure
D. Postictal paralysis
E. "Unmasking" of prior neurologic deficits in the setting of systemic illness

X-16. A 68-year-old man presents to the emergency room with right-sided face, arm, and leg weakness that began abruptly 1 hour prior to arrival. The patient is accompanied by his wife. He exhibits Broca aphasia and dysarthria. Physical examination confirms a dense hemiparesis of the right face, arm, and leg with decreased sensation. In addition, there is a gaze preference to the left. The patient's initial blood pressure on presentation to the emergency room is 220/140 and, despite treatment with IV antihypertensives, remains at 195/120. An emergent noncontrast head CT shows no evidence of intracranial hemorrhage or edema with only mild loss of gray–white matter differentiation. On further review of the patient's medical history, he has had a prior embolic stroke affecting the posterior circulation 12 months ago. He also has a history of colon cancer that was diagnosed 3 months ago when he presented with a lower gastrointestinal (GI) bleed requiring transfusion of 4 units of packed red blood cells. He successfully underwent left hemicolectomy of a stage I adenocarcinoma. Which of the following factors is a contraindication to use for IV recombinant tissue plasminogen activator in this patient?

A. Age >65
B. Blood pressure elevation >185/110
C. GI bleeding within the last 3 months
D. Major surgery within the last 3 months
E. Prior embolic stroke

X-17. All of the following are risk factors for ischemic stroke EXCEPT:

A. Diabetes mellitus
B. High-density lipoprotein cholesterol
C. Low-density lipoprotein cholesterol
D. Hypertension
E. Older age

X-18. Mr. Nielsen is in the clinic after recent discharge for an ischemic stroke. He was prescribed aspirin as a secondary prevention measure. How long does the platelet antiaggregation effect of aspirin last?

A. 12 hours
B. 1 day
C. 2–3 days
D. 6 days
E. 8 days

X-19. Mr. Fernandez is a 54-year-old man with diabetes mellitus and nonischemic cardiomyopathy with a left ventricular ejection fraction of 30% and mild, stable heart failure symptoms. He presents to the clinic today for routine follow-up and is found to have an irregularly irregular rhythm. Electrocardiogram confirms atrial fibrillation. He has no history of bleeding and has normal renal and hepatic function by laboratory studies. He lives in a rural area and reports that he will not be able to get routine blood draws easily. Which of the following is the next best therapeutic step?

A. In-office electrical cardioversion
B. Initiate amiodarone therapy
C. Initiate apixaban therapy
D. Initiate clopidogrel therapy
E. Initiate warfarin therapy

X-20. Which of the following antiplatelet agents has been proven effective in the acute treatment of ischemic stroke?

A. Aspirin
B. Clopidogrel
C. Dipyridamole
D. Prasugrel
E. Ticagrelor

X-21. You are called emergently by a nurse into an emergency department room where Mr. Freeman is a 75-year-old patient who had presented with a headache. He has just returned from head CT where an intracranial hemorrhage was found. On return from CT, he is obtunded and gurgling with arterial oxygenation saturation of 90%. He has minimal response to painful stimuli. Blood pressure is 150/90. What is the next best action?

A. Bedside craniotomy
B. IV hypertonic saline
C. Intubation and mechanical ventilation
D. Labetalol IV for blood pressure control
E. Naloxone intravenously

X-22. Mr. Gabrielle is a 74-year-old who presents with CT findings of pontine intracerebral hemorrhage. Which of the following is the most common clinical finding in pontine hemorrhage?

A. Bilateral hyper-reflexia
B. Deep coma with quadriplegia
C. Homonymous hemianopsia
D. Imbalance
E. Subtle anisocoria

X-23. Mr. Hajj is a 23-year-old previously healthy man who presents with an acute headache and altered sensorium. Head CT discovers an intracerebral hemorrhage (ICH). Which of the following is most indicated to evaluate the etiology of his ICH?

A. Ferritin and iron studies
B. Prolactin
C. Serum protein electrophoresis
D. Thyroid stimulating hormone assay
E. Urine drug screen

X-24. A 26-year-old woman has throbbing right-sided headaches that are centered around her right eye. They are worse with movement and aggravated by loud noises. There are no premonitory warning features. Triggers for the headaches include lack of sleep, stress, and red wine. A mild attack can be treated by ibuprofen, but nonsteroidal anti-inflammatory drugs have no effect on more severe pain. Which of the following best characterizes what is understood about the pathogenesis of this patient's headache syndrome?

A. Diffuse muscular contraction of the neck and scalp
B. Disinhibition of the central pacemaker neurons in the posterior hypothalamic region
C. Dysfunction of monoaminergic sensory control systems in brainstem and hypothalamus
D. Focal cerebral vasodilation in the region of the brain that is the focus of the pain
E. Vascular compression of the trigeminal nerve as it enters the pons

X-25. A 42-year-old man is evaluated for severe headaches that have occurred several times over the last 5–7 years. He describes the headache as occurring behind his left eye and coming on suddenly. The headaches have a stabbing quality and are associated with tearing of his eye and nasal congestion. He says the pain is a "12" out of 10 when it occurs, and he finds that he cannot even sit still due to pain. The headaches last about 20 minutes and then subside. He says that the headaches always seem to occur around 5 AM, but he can go months without having any headache at all. He has a difficult time identifying a trigger for the headaches. Which of the following is the most likely cause of his symptoms?

A. Cluster headache
B. Migraine
C. Paroxysmal hemicrania
D. Short-lasting unilateral neuralgiform headaches with conjunctival injection and tearing
E. Tension headache

X-26. You are seeing a 26-year-old accountant for headaches. You are trying to clinically differentiate whether these headaches are migraine or tension-type headaches. The presence of which of the following accompanying symptoms make tension-type headache much less likely?

A. Aggravation with movement
B. Nausea
C. Photophobia
D. Vomiting
E. All of the above

X-27. All of the following are effective in treating pure tension-type headaches EXCEPT:

A. Acetaminophen
B. Aspirin
C. Behavioral relaxation therapy
D. Ibuprofen
E. Triptans

X-28. A 72-year-old woman is evaluated for memory problems. She and her husband first noticed some mild problems about 2 or 3 years ago, but attributed her symptoms to "old age." They decided to seek an evaluation when she became lost while returning home from the grocery store last week. She had driven back and forth from this same store weekly for the last 20 years, and this incident frightened them both. She does not know what happened and had to call her husband for help. She has shown no changes to her personality. Her medical history is significant for hypertension and stage 2 breast cancer treated 10 years ago. She is taking ramipril 5 mg bid. She smoked one pack of tobacco daily from the age of 20 until she was 64. She drinks a glass of wine nightly. She retired from her position as an accountant at the age of 60. On examination, she appears well groomed and pleasant. Her blood pressure is 158/90 and heart rate is 82 beats/min. Her neurologic examination is normal without focal defect. Gait is normal. No rigidity is present. Neuropsychological testing shows impairment 1.5 standard deviations below the norm. Which of the following would be the most likely pathologic finding in the brain?

A. Deposition of amyloid within cerebral blood vessels
B. Loss of cortical serotonergic innervation with atrophy of the frontal, insular, and/or temporal cortex
C. Neuritic plaques and neurofibrillary tangles in the medial temporal lobes
D. Presence of intraneuronal cytoplasmic inclusions that stain with periodic acid–Schiff and ubiquitin in the substantia nigra, amygdala, cingulate gyrus, and neocortex

X-29. A 78-year-old man has been diagnosed with mild cognitive impairment after complaining of decreased memory. He asks you to prescribe something that will decrease his likelihood to progress to Alzheimer's disease. Which of the following treatments do you recommend?

A. Brain training exercises
B. Donepezil
C. Ginkgo biloba
D. Memantine
E. No treatment at this time has been demonstrated to delay the progression of mild cognitive impairment to Alzheimer disease

X-30. A 62-year-old man presents with memory and behavior problems. Until 1 year ago, he had worked as a senior account manager at a local bank, but he had to retire after he had an angry outburst with a client. He then was inappropriate with a female colleague in a departmental meeting. His family reports that this behavior was entirely out of character for him and since then, he is increasingly brusque and easily angered. He also has been overly sexual and has said many inappropriate things within the hearing of his teenage grandchildren. At the same time, it has been noted that his memory has been worsening. He has an MBA degree, but his wife has recently began managing the money after he could no longer be relied on to do this. The financial records were highly disorganized when she began to look into them. The patient also recently had a near-miss accident while driving the wrong way down a one way street. On examination, he is gruff and says that he does not want to do "this damn thing." He needs to "get the hell out of here." He was quite rude and insulting to his wife several times. He has a positive glabellar reflex. Mini-Mental State Examination is 20/30. There is no rigidity. Gait is normal. Deep tendon reflexes are 3+ and symmetric. Strength is 5/5 throughout and there are no sensory deficits. Cerebellar function is normal. Which of the following is the most likely diagnosis?

A. Alzheimer's disease
B. Dementia with Lewy bodies
C. Frontotemporal dementia
D. Progressive supranuclear palsy
E. Vascular dementia

X-31. Ms. Marann is a 75-year-old woman with 1 year of progressive memory loss. She has had difficulties with executive functioning especially over the last 6 months. You note that she has an ataxic gait and her family mentions that she has had worsening urinary incontinence as well. Neuroimaging reveals enlarged lateral ventricles (hydrocephalus) with little or no cortical atrophy. Which of the following is the most effective method of diagnosis of the likely etiology of her dementia?

A. Brain biopsy
B. Cisternography
C. Close observation after lumbar puncture and removal of 30–50 cc of cerebrospinal fluid
D. Electroencephalogram
E. Functional MRI

X-32. You are seeing a patient with progressive dementia and apathy, disinhibition, compulsivity, loss of empathy, and overeating. Brain MRI shows marked atrophy in anterior cingulate and frontoinsular region. Which of the following is an effective therapy to improve this patient's dementia?

A. Memantine
B. Phenytoin
C. Trazadone
D. Vitamin E
E. None of the above

X-33. You are seeing Ms. Wharton today, an 82-year-old woman with obesity, diabetes, hypertension, hyperlipidemia, and tobacco abuse. She has been diagnosed with vascular dementia due to multiple small strokes. Which of her following features is her STRONGEST risk factor for cardiovascular disease and stroke?

A. Age
B. Diabetes
C. Hyperlipidemia
D. Hypertension
E. Smoking

X-34. Strokes can be divided into hemorrhagic and ischemic types with subtypes within those types. Which subtype of stroke has the strongest association with cognitive impairment and vascular dementia?

A. Hemorrhagic stroke, subarachnoid subtype
B. Hemorrhagic stroke, intracerebral subtype
C. Hemorrhagic stroke, subdural subtype
D. Ischemic stroke, large vessel subtype
E. Ischemic stroke, small vessel subtype

X-35. While most cases of vascular dementia are sporadic and largely due to environmental/acquired risk factors, some are genetic. The most prevalent is cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. This disorder is due to a mutation in which of the following genes?

A. CFTR
B. Dystrophin
C. NOTCH3
D. Titin
E. Transthyretin

X-36. You are seeing Mr. DeWinter, a 71-year-old man, for changes in mental status and cognition. His wife reports that he has slowly been worsening over the last year or two. He has frequent visual hallucinations, sleeps heavily during the daytime but not well at night, and has delusions of persecution. He was noted to have some parkinsonian features previously and was started on L-dopa, but quickly developed a hallucinatory delirium requiring cessation of L-dopa. He does not have orthostatic hypotension or syncope. Which of the following diseases best fits his dementia syndrome?

A. Alzheimer's disease
B. Delirium
C. Dementia with Lewy bodies
D. Multiple systems atrophy with parkinsonism
E. Normal aging

X-37. Which of the following statements regarding Parkinson disease is TRUE?

A. Cigarette smoking reduces the risk of developing the disease.
B. Older age at presentation is more likely to be associated to genetic predisposition.
C. Parkinson disease has been identified as a monogenetic disorder related to mutations in the α-synuclein protein.
D. The hallmark pathologic feature of Parkinson disease is presence of neurofibrillary tangle and tau protein in the substantia nigra pars compacta.
E. The typical age of onset of symptoms is above 70 years.

X-38. A 64-year-old man presents with symptoms of tremor and a generalized feeling of slowing down. His tremor bothers him most on his left side. His past medical history is significant for depression, hypertension, and hyperlipidemia. He is taking fluoxetine 40 mg daily, lisinopril 40 mg daily, and atorvastatin 20 mg daily. On physical examination, he has a resting tremor with presence of cogwheel rigidity. When observing his gait, you note slow, shuffling steps with difficulty maneuvering to turn around. His facial features show decreased range of emotion and appears somewhat flat. Eye movements are full. Mental status examination shows normal mentation. You suspect Parkinson disease. Which of the following is the first choice of therapy?

A. Levodopa-carbidopa
B. Rotigotine
C. Selegiline
D. Either B or C can be used
E. Any of the above can be used

X-39. Which of the following patients with Parkinson disease is the best candidate for deep brain stimulation?

A. A 64-year-old woman on levodopa-carbidopa who continues to experience episodes of freezing while walking.
B. A 68-year-old man with recurrent falls due to orthostatic hypotension.
C. A 70-year-old woman with severe tremor unresponsive to dopaminergic therapy.
D. A 71-year-old man with worsening symptoms of dementia.
E. All of the above patients will respond to deep brain stimulation.

X-40. You are seeing Mr. Whitacre in the clinic today. He presents with rest tremor, occasional rigidity, generalized bradykinesia, and gait dysfunction with frequent falls. You would expect degeneration of which neuron subtype within the brain?

A. Dopaminergic neurons in the substantia nigra
B. GABAergic neurons in the putamen
C. Serotonergic neurons in the cortex
D. Serotonergic neurons in the substantia nigra
E. None of the above

X-41. You are seeing Mr. Williams today in the clinic. You note a tremor, which he says is new. Which of the following pathologies is matched CORRECTLY with the tremor type below:

A. Essential tremor: resting tremor.
B. Parkinson disease: action tremor.
C. Cerebellar dysfunction: resting tremor.
D. Enhanced physiologic tremor: occurs with caffeine ingestion.
E. All of the above are incorrectly matched.

X-42. You are seeing Mrs. Fajedo, a 74-year-old woman with a recently worsening tremor. She notes that it predominantly affects her hands and is worse with action such as trying to eat. It is not present at rest. It is improved by drinking 1–2 beers. She has no other symptoms. On examination, her resting heart rate is 52 beats/min (she is an avid runner and physically fit) with normal vital signs otherwise. Which of the following is the best initial therapy?

A. Bilateral hand botulinum toxin injections
B. L-dopa
C. Primidone
D. Propranolol
E. Two beers per night

X-43. You are seeing a patient with a clinical syndrome suggesting Huntington disease (HD). He is inquiring about genetic testing. Which of the following is true regarding the genetic basis of HD?

A. HD is sporadic and not genetically based.
B. HD is caused by an autosomal dominant mutation in the *aTTR* gene.
C. HD is caused by an increase in polyglutamine repeats in the *huntingtin* gene.
D. HD is caused by mutations in the *CFTR* gene.
E. HD is caused by mutations in the *LMNA* gene.

X-44. A 54-year-old man presents complaining of weakness. He has a difficult time pinpointing an onset. He believes he first noticed weakness in his right foot and leg about 6 months ago. He reports that he frequently trips over his toes and drags his foot. He also gets frequent cramps when he stretches in bed in the mornings. The weakness is progressing to involve both legs now. On examination, you note tongue fasciculations. Deep tendon reflexes are 3+ at the knees and ankles. Strength is 4– at the extensors and flexors of the right foot and 4+ at the left foot. Hand grip strength is also 4+. Which of the following is the suspected pathologic lesion(s)?

A. Degeneration of the corticospinal tracts
B. Demyelinating plaques
C. Loss of anterior horn cells in the spinal cord
D. Loss of large pyramidal cells in the precentral gyrus
E. Lymphocytic infiltrate of spinal roots and nerves
F. A and C

X-45. You are seeing a 14-year-old girl for worsening muscle weakness. On examination, she has weakness of the proximal muscles of her arms and legs with mild atrophy. Creatine kinase levels are not elevated and muscle biopsy demonstrates denervation pattern atrophy. You should suspect which of the following diseases?

A. Duchenne muscular dystrophy
B. Emery-Dreifuss muscular dystrophy
C. Limb-girdle muscular dystrophy
D. Mitochondrial encephalopathy, lactic acidosis, and stroke-like symptoms
E. Spinal muscular atrophy

X-46. You are seeing a patient with a recent diagnosis of Creutzfeldt-Jakob disease (CJD). Which of the following is true regarding the pathogen responsible for CJD?

A. It is caused by a bacterial pathogen.
B. It is caused by a DNA virus.
C. It is caused by a transmissible pathogen devoid of nucleic acid.
D. It is caused by an environmental toxin.
E. It is caused by an RNA virus.

X-47. Mr. Rollins is brought to the emergency department on Saturday night. His wife reports that he came home from a late business meeting with altered mental status and ataxia. He was completely normal this afternoon when she visited him at work. On examination, you note that he is moderately somnolent but awakens with voice. He has a bilateral ataxia, which is symmetric. He denies vertigo. Which of the following tests is most likely to discover the etiology of his neurologic abnormalities?

A. Blood ethanol level
B. Brain MRI focusing on fine cuts through the cerebellum
C. Dix-Hallpike test
D. Lumbar puncture with polymerase chain reaction for varicella zoster
E. Spinal MRI

X-48. A 62-year-old woman is evaluated for symptoms of "slowing down." She used to be very active and ran 2–4 miles at least 3 days per week. For the last 6 months, she has not been able to complete even 1 mile, and her husband feels she has been moving more slowly and with a shuffling gait. She reports no tremor. She frequently feels lightheaded on standing and has been evaluated in the emergency department twice for falls that occurred soon after standing with presyncope symptoms. After one fall, she did require sutures for a scalp laceration. She has also been experiencing significant constipation requiring daily treatment with polyethylene glycol and bisacodyl suppositories. On physical examination, she has a blood pressure of 122/78 and a heart rate of 72 beats/min while seated. On standing, her blood pressure falls to 92/60 with a heart rate of 102 beats/min. She does report dizziness with the maneuver. She has bradykinesia and walks with a shuffling gait. Cranial nerves are intact with full eye movements. Deep tendon reflexes are 2+ and symmetric. There is rigidity with passive motion of the forearms. She has no tremor. Mental status examination is normal. Which of the following is the most likely diagnosis?

A. Diffuse Lewy body disease
B. Multiple system atrophy
C. Parkinson disease
D. Postural orthostatic tachycardia syndrome
E. Progressive supranuclear palsy

X-49. A 58-year-old woman is seen for recurrent episodes of very sharp pain lasting about 1 minute over her right cheek and lips. These pain episodes occur in clusters with intense pain. When an episode occurs, it is present both day and night and can recur over a period of about a week. Paroxysms of pain can be elicited by washing her face. On physical examination, there is no sensory or motor loss in the right face. There are no masses. Touching the right face does bring about an episode of pain for the patient. Which of the following is the next best step in management of this patient?

A. Initiate treatment with carbamazepine 100 mg with a goal dose of 200 mg qid
B. Perform an MRI/MR angiography of the brain
C. Refer patient for a temporal artery biopsy
D. Refer patient for electromyography and nerve conduction study
E. Refer patient for microvascular decompression surgery

X-50. You are evaluating Mr. Brodshaw, a 24-year-old graduate student with no past medical history. He presents with abrupt left-sided facial weakness. On examination, he has Bell's palsy. Which of the following pathologic entities is the most common cause of Bell's palsy?

A. Cerebral neoplasm
B. Herpes simplex 1
C. Lyme disease
D. Trauma
E. Varicella-zoster virus

X-51. On your evaluation of a 24-year-old with unilateral facial weakness, you diagnose a simple Bell's palsy without any other neurologic deficits. Laboratory studies including an erythrocyte sedimentation rate, Lyme titer, and angiotensin-converting enzyme level are normal. Chest x-ray is normal. Which of the following is the next most reasonable therapeutic step?

A. IV Ig infusion
B. Focused muscle electrical stimulation
C. L-dopa therapy
D. Prednisone 60 mg daily for 5 days and then tapered over 5 days
E. Surgical decompression of the seventh cranial nerve

X-52. A 65-year-old woman with a prior history of stage IIB carcinoma of the right breast presents with a 1-week history of sharp mid-back pain. She reports that it becomes worse with movement and coughing. She has not slept well because the pain has awakened her. On the day of presentation, she developed weakness in her lower extremities such that she is not able to bear weight. She has had incontinence of the bladder over the last day. On examination, the patient has tenderness to palpation over the lower thoracic spine. The strength in the lower extremities is 3 out of 5 with decreased deep tendon reflexes bilaterally. Anal sphincter tone is decreased. Sensation to light touch and pinprick also demonstrates a decrease in perception to the level of T8. Metastatic disease to the spine is demonstrated in multiple thoracic and lumbar vertebral bodies with cord compression at T8 on T1-weighted MRI. Which of the following is the next best step(s) in the management of this patient?

A. Administer dexamethasone 10 mg IV every 6 hours
B. Consult medical oncology for additional chemotherapy
C. Consult neurosurgery for surgical decompression
D. Consult radiation oncology for urgent radiotherapy
E. A and C
F. A, B, and D
G. All of the above

X-53. A 32-year-old African American man presents to the emergency room with progressive lower extremity weakness that has been present for the last month. It has now progressed to the point that he is unable to bear weight. He also has been experiencing loss of sensation and aching pains in his mid-back. He also has experienced a sensation of incomplete voiding with mild urinary incontinence. Today, he also had incontinence of stool. His past medical history is significant for a stab wound to the left chest 9 months prior that required surgical repair. A CT was negative at that time for any lymph node abnormalities. He is on no medications and does not smoke or drink alcohol. Physical examination confirms lower extremity paresis with strength only 3/5 and decreased deep tendon reflexes. Sensation to light touch and pinprick is absent in the lower extremities. He develops sensory perception at the umbilicus. An MRI shows multilevel enhancement of the spinal cord consistent with edema. It has a predominance in the mid-thoracic spinal cord. Gadolinium administration shows enhancement in a nodular fashion of the surface of the cord. Lumbar puncture is performed. There are 32 white blood cells (WBCs)/μL in the first tube and 24 WBCs/μL in the fourth tube. These are 90% lymphocytes. The cerebrospinal fluid protein level is 75 mg/dL. The glucose level is normal. A chest radiograph demonstrates enlargement of the hilar lymph nodes without pulmonary infiltrates. On chest CT, bilateral hilar, subcarinal, and pre-carinal lymphadenopathy is observed with the largest lymph node measuring 2 × 1.8 cm. Serum calcium is 12.5 mg/dL. A biopsy of the hilar lymph nodes is planned. Which of the following is the most likely finding on biopsy?

A. Abundant atypical lymphocytes that demonstrate clonality on flow cytometry.
B. Caseating granulomatous inflammation.
C. Noncaseating granulomatous inflammation.
D. Nonspecific chronic inflammatory changes.
E. Sheets of small, round cells with dark nuclei, scant cytoplasm, and salt and pepper chromatin with indistinct nucleoli; frequent mitotic figures are also seen.

X-54. A 27-year-old woman presents for neurologic evaluation after experiencing a severe burn on the palm of her right hand. She had placed her hand onto the hot surface of a smooth electric range. She did not feel the burn when it occurred and only when she picked her hand up did she notice the burn. After that, it was discovered that the patient unknowingly has bilateral loss of pain and temperature sensation in both hands. However, she does have touch and vibratory sense. Mapping of her loss of sensation shows decreased pain sensation in the nape of her neck, shoulders, and upper arms as well in a cape-like distribution. Deep tendon reflexes are absent at the biceps and triceps, and there is visible muscle wasting of the right biceps and shoulder musculature. Which of the following is the most likely diagnosis?

A. Arteriovenous malformation of the spine
B. Neoplastic spinal cord compression
C. Subacute combined degeneration
D. Syringomyelia
E. Transverse myelitis

X-55. Which of the following medications used to treat multiple sclerosis is highly effective and targets CD20 on the surface of mature B cells?

A. Dimethyl fumarate
B. Fingolimod
C. Interferon beta
D. Natalizumab
E. Ocrelizumab

X-56. A 31-year-old white woman is evaluated for symptoms of blurred vision and weakness. She is not really sure how long the symptoms have been occurring. She has had intermittent blurring of her vision for the last 2 months, although it has been more persistent for the last 2 weeks. She states that she also notes that colors seem less vivid and that her symptoms are worse in the right eye. Three months ago, she did notice some sharp pains in the right eye that were worse when she looked around. They subsided after about a week, and since then, her vision has worsened. At the same time, she feels as though she is stiff in her legs and also feels that her left leg is weak. She sometimes feels as if her left leg will give out on her if she stands on it for a prolonged period. Her past medical history is significant for type 1 diabetes mellitus for which she uses an insulin pump. She has smoked one pack of cigarettes daily since the age of 18. On physical examination, there is spasticity in both of her lower extremities with passive motion. Deep tendon reflexes are 3+ bilaterally with strength at the quadriceps on the right at 4/5. All other strength in the lower extremity is 5/5 bilaterally. Sensation to light touch and pinprick is decreased in the lower extremities. A dilated funduscopic examination shows swelling of the optic disc. Which of the following findings is most likely to be demonstrated?

A. Elevated protein levels in the cerebrospinal fluid to more than 100 mg/dL
B. Hyperintensity on T1-weight images consistent with a mass lesion in the occipital lobe with hydrocephalus
C. Hyperintensity on T2-weighted MRI images in multiple areas of the brain, brainstem, and spinal cord
D. Marked increase in transmission of somatosensory evoked potentials of lower limbs
E. Presence of 15 polymorphonuclear cells per microliter in the cerebrospinal fluid

X-57. In the patient in question X-56, the expected finding is demonstrated on testing. On further historical review, the patient reports that she had one prior episode of blurred vision that resolved spontaneously about 8 months ago. She never sought treatment for it, although it lasted for about 2 weeks. You make the correct diagnosis. All of the following are epidemiologic risks factors for her disease EXCEPT:

A. Age between 20 and 40
B. Cigarette smoking
C. Female sex
D. History of an autoimmune disorder (type 1 diabetes mellitus)
E. White race

X-58. Which of the following is the target of the autoantibody found in 70% of patients with a clinical diagnosis of neuromyelitis optica?

A. Aquaporin-4
B. Cyclic citrullinated peptides
C. Double-stranded DNA
D. Myeloperoxidase
E. tRNA synthetase

X-59. Which of the following distinguish neuromyelitis optica (NMO) clinically from multiple sclerosis (MS)?

A. Attacks of optic neuritis can be bilateral and produce severe vision loss more commonly in NMO than in MS.
B. Brain MRIs are always normal in NMO.
C. Myelitis can be severe and transverse in NMO, but is rare in MS.
D. NMO is more common in men, whereas MS is more common in women.
E. A and C are true.

X-60. A 40-year-old woman with systemic lupus erythematosus (SLE) presents to the clinic with proximal and distal leg weakness and sensory loss in her feet that has been present for several months. She has not had pain or burning in her feet, just decreased sensation. She has been treated with hydroxychloroquine and mycophenolate mofetil for 10 years for her SLE. She does not take other medications. Electromyography demonstrates myopathic muscle action potentials in the proximal muscles and reduced recruitment in more distal muscles. Nerve conduction study shows a reduction in amplitude. Lumbar puncture does not show elevated protein or white blood cells. Which of the following is the most likely cause of her neurologic symptoms?

A. Chronic inflammatory demyelinating polyneuropathy
B. Guillain-Barré syndrome
C. Hydroxychloroquine toxicity
D. Multiple sclerosis
E. Small fiber neuropathy from SLE

X-61. All of the following are known to cause radiculopathy EXCEPT:

A. Diabetes mellitus
B. Herniated disk
C. Lyme disease
D. Sarcoidosis
E. Vitamin B_6 deficiency

X-62. A 24-year-old man presents for evaluation of foot drop. He has noted that for the last several months he has had difficulty picking his feet up to walk upstairs and over thresholds. His right leg is more affected than his left leg. He has not noted any sensory changes. His father and paternal aunt each have had some weakness in their lower extremities; however, his father is currently 50 years of age and only began to develop some weakness in the last 2 years. His paternal aunt has always had a limp for as long as he can recall. He does not remember his grandparents having any symptoms, although his paternal grandfather died in a car accident at the age of 46 prior to his birth. The patient's examination is notable for distal leg weakness with reduced sensation to light touch in both lower extremities. Knee and ankle jerk reflexes are unobtainable. Calves are reduced in size bilaterally. Upper extremity examination is normal. Which of the following is the most likely diagnosis?

A. Charcot-Marie-Tooth syndrome
B. Fabry disease
C. Guillain-Barré syndrome
D. Hereditary neuralgic amyotrophy
E. Hereditary sensory and autonomic neuropathy

X-63. A 52-year-old woman with long-standing poorly controlled type 2 diabetes mellitus is evaluated for a sensation of numbness in her fingers and toes, as if she is wearing gloves and socks all the time. She also reports tingling and burning in the same location, but no weakness. Her symptoms have been intermittently present for the last several months. After a thorough evaluation, nerve biopsy is obtained and demonstrates axonal degeneration, endothelial hyperplasia, and perivascular inflammation. Which of the following statements regarding this condition is true?

A. Autonomic neuropathy is rarely seen in combination with sensory neuropathy.
B. The presence of retinopathy or nephropathy does not portend increased risk for diabetic neuropathy.
C. This is the most common cause of peripheral neuropathy in developed countries.
D. Tight glucose control will reverse her neuropathy.
E. None of the above is true.

X-64. Which of the following statements is true regarding the treatment of Guillain-Barré syndrome?

A. Glucocorticoids are first-line therapy.
B. Combination IVIg and plasma exchange has better efficacy than either treatment alone.
C. Effective therapy is equally effective regardless of how quickly it is given after first motor symptoms.
D. IVIg and plasma exchange are both effective and either can be used as first-line therapy.
E. No therapy reduces the likelihood of mechanical ventilation.

X-65. A 52-year-old man presents to the emergency department complaining of weakness that has developed over the last 2 days. He first noticed that he had generalized fatigue and felt like he was having a hard time moving his feet. Over the last 24 hours, the weakness has progressed to the point that he can barely stand with assistance. He was brought into the emergency department in a wheelchair. He is beginning to feel that it is difficult to lift his arms. He also complains of a sharp pain in his shoulders and along his spine. Both his hands and feet are tingling. On physical examination, his initial blood pressure is 138/82. On repeat 1 hour later, it is 92/50. His heart rate is 108 beats/min, respiratory rate is 24 breaths/min, temperature is 37.0°C (98.6°F), and SaO_2 is 96% on room air. He appears anxious and weak. Deep tendon reflexes are absent at the knee, ankle, and wrist. The brachioradialis reflex is 1+. Strength throughout the lower extremities is diminished as the patient is unable to lift either leg against gravity. In the arms, strength is 4/5 in the deltoids, biceps, and triceps. However, he is unable to maintain a grip, and wrist flexion and extension are 3/5. Which of the following features would most commonly accompany this patient's history?

A. A diagnosis of "walking pneumonia" that was treated with azithromycin 2 weeks prior to presentation
B. An acute diarrheal illness 2 weeks prior to presentation
C. Presence of a massive mediastinal lymphadenopathy on chest radiograph
D. Presence of a monoclonal gammopathy of unknown significance on laboratory testing
E. Recent immunization with the H1N1 vaccine

X-66. A 34-year-old woman is seen for complaints of weakness for the last month. She notes this to be particularly worse in the late afternoon and evening. Initially, she attributed the weakness to stress from her job, but she feels that the weakness is worsening despite taking several days off work. She also is now noticing some occasional double vision, and her husband has noticed that her voice sounds weak. The patient denies pain. On physical examination, you note the appearance of mild ptosis and a nasal, breathy tone to her voice. Which of the following tests would be most sensitive and specific for making a diagnosis in this patient?

A. Acetylcholine receptor antibodies
B. Edrophonium test
C. Muscle-specific kinase antibodies
D. Repetitive nerve stimulation test
E. Voltage-gated calcium channel antibodies

X-67. Which of the following conditions can be associated with myasthenia gravis?

A. Chronic kidney disease
B. Diabetes mellitus
C. Rheumatoid arthritis
D. Thymoma
E. C and D

X-68. A 40-year-old woman with a 2-year history of generalized myasthenia gravis presents to the clinic with worsening symptoms. Her voice is weaker and she is having trouble climbing stairs. She has been on pyridostigmine 60 mg three times a day since her initial diagnosis. On physical examination she has ptosis. Her forced vital capacity is 90% predicted. What is the next-line treatment for her myasthenia?

A. Azathioprine
B. IVIg
C. Mycophenolate mofetil
D. Plasmapheresis
E. Thymectomy

X-69. Which of the following endocrinopathies can cause an elevated creatine kinase up to 10 times the upper limit of normal?

A. Hyperaldosteronism
B. Hyperparathyroidism
C. Hyperthyroidism
D. Hypoparathyroidism
E. Hypothyroidism

X-70. In addition to causing a toxic myopathy, which of the following drugs may trigger an immune-mediated necrotizing myopathy associated with anti-HMG-CoA-reductase antibodies?

A. Atorvastatin
B. Gemfibrozil
C. Glucocorticoids
D. Niacin
E. Zidovudine

X-71. A 34-year-old woman seeks evaluation for weakness. She reports tripping when walking for the last 2 years that she feels is due to weakness in her left lower leg. She also has recently begun to drop things, once allowing a full cup of coffee to spill onto her legs. The patient also feels as if the appearance of her face has changed over the course of many years, stating that she feels as if her face is becoming more hollow and elongated although she has not lost any weight recently. She has not seen a physician in many years and has no relevant past medical history. Her only medications are a multivitamin and calcium with vitamin D. Her family history is significant for similar symptoms of weakness in her brother who is 2 years older. Her mother, who is 58 years old, was diagnosed with mild weakness after her brother was evaluated but is not symptomatic. On physical examination, the patient's face appears long and narrow with wasting of the temporalis and masseter muscles. Her speech is mildly dysarthric, and the palate is high and arched. Strength is 4/5 in the intrinsic muscles of the hand, wrist extensors, and ankle dorsiflexors. After testing handgrip strength, you notice that there is a delayed relaxation of the muscles of the hand. Which of the following is the most likely diagnosis?

A. Acid maltase deficiency (Pompe disease)
B. Becker muscular dystrophy
C. Duchenne muscular dystrophy
D. Myotonic dystrophy
E. Nemaline myopathy

X-72. All of the following are predisposing factors to the development of chronic fatigue syndrome EXCEPT:

A. Childhood emotional abuse
B. Male gender
C. Physical inactivity during childhood
D. Premorbid hyperactivity
E. Premorbid psychiatric illness

X-73. Which of the following interventions have been effective in improving symptoms of the chronic fatigue syndrome?

A. Acyclovir
B. Cognitive behavioral therapy
C. Gabapentin
D. Psychoanalysis
E. Venlafaxine

X-74. All of the following statements regarding autism spectrum disorders (ASDs) are true EXCEPT:

A. ASD is monogenically inherited with mutations in a single gene responsible for nearly all cases.
B. ASDs have a high concordance rate in monozygotic twins.
C. First-degree relatives of a patient with ASDs have a 10-fold higher risk of ASD than the general population.
D. Gene mutations that are associated with ASD tend to be in genes responsible for proteins involved in synaptic function.
E. All of the above are true.

X-75. A 34-year-old woman seeks evaluation because of insomnia. She reports difficulty both falling and staying asleep because she cannot calm her mind. When questioned, she says she has always been a worrier. You are considering a diagnosis of generalized anxiety disorder. All of the following characteristics are common in this disorder EXCEPT:

A. She has episodic palpitations and shortness of breath lasting 10–30 minutes associated with feelings of impending doom.
B. She particularly worries about her job as a data analyst at a major telecommunications company, and she frequently avoids social outings because she "freezes" in social situations.
C. She reports concomitant feelings of hopelessness and sadness and worries about death.
D. She reports drinking four glasses of wine or more nightly to calm herself prior to bed.
E. Symptoms began during her teenage years.

X-76. You are paged by the clinic staff covering the sleep laboratory. A 24-year-old man has walked into the sleep laboratory asking if a sleep study will help him understand where the voices in his head are coming from. The staff says he appears somewhat agitated and is talking to himself. You arrived to the sleep laboratory to find a disheveled-appearing young man pacing in the lobby. When you attempt to speak with him, he says that he has been hearing an angry voice telling him that he is a worthless pig. It gets loudest whenever he is lying in bed. Sometimes it tells him he is a demon and to hurt himself. He says these voices are being sent into his brain by an alien satellite and thinks a sleep study will help show the abnormal brain waves that are not his, since the voices are worse at night. His speech is pressured and he speaks rapidly, pacing the entire time. He refuses to go to the emergency room for help. You call 911 as it is obvious that the patient is having active hallucinations. The man is unwilling to provide any medical history or even his last name. He is admitted involuntarily to a psychiatric facility and diagnosed with acute psychosis and eventually schizophrenia as this was his first episode of psychosis. He is treated appropriately with antipsychotics. Which of the following statements regarding his prognosis is TRUE?

A. Antipsychotics are effective in treating 95% of patients with a first episode of psychosis.
B. Full remission from an episode of psychosis typically takes 3–6 months.
C. If medications are discontinued, the relapse rate is 60% at 6 months.
D. More than 25% of schizophrenia patients commit suicide.
E. Prognosis depends on severity of symptoms at initial presentation.

X-77. A 26-year-old woman presents to the emergency room complaining of shortness of breath and chest pain. These symptoms began abruptly while at a shopping mall and became progressively worse over 10 minutes prompting her to call 911. Over this same period, the patient describes feeling her heart pounding, and she states that she felt like she was dying. She feels lightheaded and dizzy. It is currently about 20 minutes since the onset of symptoms, and the severity has abated although she is not back to her baseline. She denies any immediate precipitating cause although she has been under increased stress as her mother has been hospitalized recently with advanced breast cancer. She has never had any episode like this previously. She does not take any medications and has no medical history. She denies tobacco, alcohol, or drug use. On initial examination, she appears somewhat anxious and diaphoretic. Her initial vital signs show a heart rate of 108 beats/min, blood pressure of 122/68, and respiratory rate of 20 breaths/min. She is afebrile. Her examination is normal. Her arterial blood gas shows a pH of 7.52, $PaCO_2$ 28 mmHg, and PaO_2 116 mmHg. The electrocardiogram shows sinus tachycardia. A D-dimer is normal. Which of the following is the next best step in the management of this patient?

A. Initiate therapy with alprazolam 0.5 mg as needed
B. Initiate therapy with fluoxetine 20 mg daily
C. Perform a CT pulmonary angiogram
D. Reassure the patient and suggest medical and/or psychological therapy if symptoms recur on a frequent basis
E. Refer for cognitive behavioral therapy

X-78. All of the following antidepressant medications are correctly paired with its class of medication EXCEPT:

A. Duloxetine: selective serotonin reuptake inhibitor
B. Fluoxetine: selective serotonin reuptake inhibitor
C. Nortriptyline: tricyclic antidepressant
D. Phenelzine: monoamine oxidase inhibitor
E. Venlafaxine: mixed norepinephrine/serotonin reuptake inhibitor and receptor blocker

X-79. A 42-year-old woman seeks your advice regarding symptoms concerning for post-traumatic stress disorder. She was the victim of a home invasion 6 months previously where she was robbed and beaten by a man at gunpoint. She thought she was going to die and was hospitalized with multiple blunt force injuries including a broken nose and zygomatic arch. She now states that she is unable to be alone in her home and frequently awakens with dreams of the event. She is irritable with her husband and children and cries frequently. She has worsening insomnia and often stays awake most of the night watching out her window because she is afraid her assailant will return. She has begun drinking a bottle of wine nightly to help her fall asleep, although she notes that this has worsened her nightmares in the early morning hours. You concur that post-traumatic stress disorder is likely. Which of the following treatments do you recommend for this patient?

A. Avoidance of alcohol
B. Cognitive behavioral therapy
C. Paroxetine 20 mg daily
D. Trazodone 50 mg nightly
E. All of the above

X-80. A 36-year-old man is being treated with venlafaxine 150 mg twice daily for major depression. He has currently been on the medication for 4 months. After 2 months, his symptoms were inadequately controlled necessitating an increase in the dose of venlafaxine from 75 mg twice daily. He had one prior episode of major depression when he was 25. At that time, he was treated with fluoxetine 80 mg daily for 12 months, but found the sexual side effects difficult to tolerate. He asks when he can safely discontinue his medication. What is your advice to the patient?

A. He should continue on the medication indefinitely as his depression is likely to recur.
B. The current medication should be continued for a minimum of 6–9 months following control of his symptoms.
C. The medication can be discontinued safely if he establishes a relationship with a psychotherapist who will monitor his progress and symptoms.
D. The medication can be discontinued safely now as his symptoms are well controlled.
E. The medication should be switched to fluoxetine to complete 12 months of therapy as this was previously effective for him.

X-81. You are admitting a 24-year-old woman with recurrent gastrointestinal (GI) bleeds. On reviewing her medical records, it becomes evident that she has repeatedly switched physician care teams. She has had over 20 admissions for bright red blood in her stool and mild anemia. After 6 colonoscopies and 10 upper endoscopies (including push and double balloon enteroscopies), no source of bleeding has been found. When a physician begins to question the organic nature of her purported GI bleeding, she transitions to a new physician. You suspect Munchausen syndrome. Which of the following is the best treatment strategy?

A. Confrontation where you calmly but clearly tell her you believe she is faking her GI bleeds.
B. During discussion on the cause of her illness, introduce psychological causation as one of a number of possible explanations.
C. Offer repeated upper endoscopy whenever the patient has hematochezia and anemia.
D. Perform a repeat endoscopy and tell the patient you found a bleeding ulcer (even if you do not).
E. Provide the patient with your home phone number and encourage calls whenever she feels distressed.

X-82. You are seeing a 28-year-old man in your primary care clinic. He reports drinking alcohol on most days. Typically, he drinks 3–4 beers daily, but on weekends, he drinks as much as 8–12 beers per night. He has not missed work due to his drinking, although he does state that he has been hungover at work at least twice in the last month. He also has blacked out from binge drinking at least once in the last 6 months. However, he does not feel that he has any problem with alcohol. He states he never drinks and drives and has not ever felt guilt related to his drinking. You suspect he may be minimizing his level of alcohol consumption. Which of the following laboratory tests has the greatest sensitivity and specificity in identifying heavy alcohol consumption?

A. Aspartate aminotransferase elevated >2 times alanine aminotransferase
B. Carbohydrate-deficient transferrin >20 U/L or 2.6%
C. Gamma-glutamyl transferase >35 U/L
D. Mean corpuscular volume >91 μm^3
E. A and D
F. B and C

X-83. Which of the following will lead to a faster rate of absorption of alcohol from the gut into the blood?

A. Co-administration with a carbonated beverage
B. Concentration of alcohol of more than 20% by volume
C. Concurrent intake of a high carbohydrate meal
D. Concurrent intake of a high fat meal
E. Concurrent intake of a high protein meal

X-84. Which of the following best reflects the effect of alcohol on neurotransmitters in the brain?

A. Decreases dopamine activity
B. Decreases serotonin activity
C. Increases gamma-aminobutyric acid activity
D. Stimulates muscarinic acetylcholine receptors
E. Stimulates N-methyl-D-aspartate excitatory glutamate receptors

X-85. In an individual without any prior history of alcohol intake, what serum concentration of ethanol (in grams per deciliter) would likely result in death?

A. 0.02
B. 0.08
C. 0.28
D. 0.40
E. 0.60

X-86. A 42-year-old man with alcohol dependence is admitted to the hospital for acute pancreatitis. On admission, he has an abdominal CT that shows edema without necrosis or hemorrhage of the pancreas. He is treated with IV fluids with dextrose, multivitamins, thiamine 50 mg daily, pain control, and bowel rest. He typically drinks 24 12-ounce beers daily. Forty-eight hours after admission, you are called because the patient is febrile and combative with the nursing staff. His vital signs demonstrate a heart rate of 132 beats/min, blood pressure of 184/96, respiratory rate of 32 breaths/min, temperature of 38.7°C (101.7°F), and oxygen saturation of 94% on room air. He is agitated, diaphoretic, and pacing his room. He is oriented to person only. His neurologic examination appears nonfocal, although he does not cooperate. He is tremulous. Which of the following is the next step in the management of this patient?

A. Administration of a bolus of 1 L normal saline and thiamine 100 mg IV.
B. Administration of diazepam 10–20 mg IV followed by bolus doses of 5–10 mg as needed until the patient is calm but arousable.
C. Perform an emergent head CT.
D. Perform two peripheral blood cultures and begin treatment with imipenem 1 g IV every 8 hours.
E. Place the patient in four-point restraints and treat with haloperidol 5 mg IV.

X-87. A 48-year-old woman is recovering from alcohol dependence and requests medication to help prevent relapse. She has a medical history of stroke occurring during a hypertensive crisis. Which of the following medications could be considered?

A. Acamprosate
B. Disulfiram
C. Naltrexone
D. A and C
E. Any of the above

X-88. In 2015, approximately how many deaths were attributed to opioid overdose in the United States?

A. 200
B. 2000
C. 20,000
D. 200,000
E. 2,000,000

X-89. You are taking care of a 24-year-old who is admitted with methicillin-resistant *Staphylococcus aureus* bacteremia. About 10 hours after admission, you note that he has excessive lacrimation and is yawning repeatedly. His nose is running and he is mildly diaphoretic. Sometime later, you note restlessness and he becomes nauseated and has emesis. You expect he is withdrawing from which of the following illicit substances?

A. Alcohol
B. Cocaine
C. Marijuana
D. Methamphetamines
E. Opioids

X-90. Which of the following accurately matches the direction of change experienced in respective pituitary hormone from opioid use?

A. Prolactin: decrease
B. Luteinizing hormone: increase
C. Thyrotropin: increase
D. Growth hormone: increase
E. Corticotropin-releasing factor: increase

X-91. You are called to the room emergently for hypoxic respiratory failure. On arrival, you find a 42-year-old man who had suffered a femur fracture and undergone surgical reduction and fixation. He is near comatose, with a respiratory rate of 4 breaths/min and oxygen saturation of 60%. The nurse notes that she gave him 1 mg of IV hydromorphone 20 minutes ago, but on review of the medication administration record it rapidly becomes apparent that 10 mg of IV hydromorphone was given accidently. You administer IV naloxone and the patient awakens, and his respiratory rate and oxygen saturations normalize. However, 10 minutes later, he again becomes obtunded and hypopneic. Which of the following is the next best step?

A. Administer IV flumazenil
B. Check serum electrolytes
C. Intubate and transfer to the intensive care unit
D. Obtain emergent head CT
E. Start a naloxone drip

X-92. All of the following are complications of cocaine use EXCEPT:

A. Arterial vasoconstriction
B. Increased myocardial oxygen demand
C. Tachycardia
D. Thrombosis
E. All of the above are complications of cocaine use

X-93. A patient presents to you with concerns for addiction to *Salvia divinorum*. You recommend which of the following for therapy of his addiction?

A. Acamprosate
B. Alprazolam
C. Behavioral therapy
D. Fluoxetine
E. Naloxone

X-94. Which of the following statements about cigarette smoking is true?

A. Approximately 75% of cigarette smokers will die prematurely due to cigarette smoking unless they are able to quit.
B. Approximately 90% of peripheral vascular disease in non-diabetic individuals is attributable to cigarette smoking.
C. Cigarette smoking causes small airway inflammation and alveolar destruction sufficient to cause clinical symptoms in about 40% of smokers.
D. More than one-half of smokers attempted to quit in the last year, and of these, 25% remained not smoking for 6 months or more.
E. Two of every five deaths in the United States can be attributed to cigarette use.

X-95. A 42-year-old woman presents for a yearly office visit. She is in general good health and takes no medications. Her body mass index is 32 kg/m^2. She was previously treated for depression with sertraline 100 mg daily for 12 months. She last took the medication 6 months ago. She is feeling mentally healthy now. She has smoked since the age of 21 and smokes one pack of cigarettes daily. You advise her to quit smoking. She tells you she has been thinking about this a lot lately since her father, who was a smoker, died 2 years ago at the age of 74 from complications of lung cancer. She previously has tried on her own, both “cold turkey” and using nicotine patches. She was unable to sustain abstinence longer than a month. The only time she had sustained abstinence was when she was pregnant 18 years ago, but she quickly started again after delivery. Which of the following do you recommend for this patient?

A. Close follow-up with ongoing counseling
B. Nicotine replacement therapy with patches or nasal inhaler
C. Varenicline orally
D. A and B only
E. A combined with either B or C is an acceptable option

X-96. You are counseling your patient on the need to quit smoking cigarettes. She has been smoking for over two decades and wants to quit to avoid the harmful physical effects of smoking. Wanting to take "baby steps," she has switched to low-tar, low-nicotine cigarettes. Which of the following statements regarding the potential benefit of switching to these low-yield cigarettes is true?

A. Fewer smoking-drug interactions are found among smokers of low-yield cigarettes.
B. Most smokers inhale the same amount of nicotine and tar even if they switch to low-yield cigarettes.
C. Smokers of low-yield cigarettes tend to inhale less deeply and smoke fewer cigarettes daily.
D. Smoking low-yield cigarettes decreases the harmful cardiovascular effects of cigarette smoking.
E. Smoking low-yield cigarettes is a reasonable alternative to complete smoking cessation for chronic smokers.

ANSWERS

X-1. **The answer is E.** *(Chap. 415)* The first priority is to identify the region of the nervous system that is likely to be responsible for the symptoms. Localization is usually possible from the history and physical examination. Errors commonly result from an overreliance on costly neuroimaging procedures and laboratory tests, which, while useful, do not substitute for an adequate history and neurologic examination. The proper approach begins with the patient and focuses the clinical problem first in anatomic and then in pathophysiologic terms; only then should a specific neurologic diagnosis be entertained. Deciding "where the lesion is" accomplishes the task of limiting the possible etiologies to a manageable, finite number. In addition, this strategy safeguards against making serious errors. For example, symptoms of recurrent vertigo, diplopia, and nystagmus should not trigger "multiple sclerosis" as an answer (etiology) but "brainstem" or "pons" (location); then a diagnosis of brainstem arteriovenous malformation will not be missed for lack of consideration.

X-2. **The answer is C.** *(Chap. 415)* In the neurological examination, orientation is tested by asking the person to state his or her name, location, and time (day of the week and date); time is usually the first to be affected in a variety of conditions. Simply asking these questions also allows initial assessment of speech and language. Speech is assessed by observing articulation, rate, rhythm, and prosody (i.e., the changes in pitch and accentuation of syllables and words). Language is further assessed by observing the content of the patient's verbal and written output, response to spoken commands, and ability to read. A typical testing sequence is to ask the patient to name successively more detailed components of clothing, a watch, or a pen; repeat the phrase "No ifs, ands, or buts"; follow a three-step, verbal command; write a sentence; and read and respond to a written command.

X-3. **The answer is D.** *(Chap. 416)* Numerous noninvasive imaging options are available to clinicians evaluating patients with neurologic disorders (Table X-3). These include CT and variations CT angiography, perfusion CT, and dual energy CT and MRI and variations MR angiography, MR vessel wall imaging, functional MRI, MR spectroscopy, MR neurography, diffusion and diffusion tensor MR imaging, susceptibility-weighted MR imaging, arterial spin label imaging, and perfusion MRI. For suspected white matter disorders including suspected demyelinating disease, MRI with contrast is the best first imaging test.

X-4. **The answer is C.** *(Chap. 416)* Contrast nephropathy is not common. Acute kidney injury may result from hemodynamic changes, renal tubular obstruction and cell damage, or

TABLE X-3 **Guidelines for the Use of CT, Ultrasound, and MRI**

Condition	Recommended Technique
Hemorrhage	
Acute parenchymal	CT, MRI
Subacute/chronic	MRI
Subarachnoid	CT, CTA, lumbar puncture → angiography
Aneurysm	Angiography > CTA, MRA
Ischemic infarction	
Hemorrhagic infarction	CT or MRI
Bland infarction	MRI with diffusion > CT, CTA, angiography
Carotid or vertebral dissection	MRI/MRA
Vertebral basilar insufficiency	CTA, MRI/MRA
Carotid stenosis	CTA, MRA > US
Suspected mass lesion	
Neoplasm, primary or metastatic	MRI + contrast
Infection/abscess	MRI + contrast
Immunosuppressed with focal findings	MRI + contrast
Vascular malformation	MRI ± angiography
White matter disorders	MRI
Demyelinating disease	MRI ± contrast
Dementia	MRI > CT
Trauma	
Acute trauma	CT
Shear injury/chronic hemorrhage	MRI + susceptibility-weighted imaging
Headache/migraine	CT/MRI
Seizure	
First time, no focal neurologic deficits	MRI > CT
Partial complex/refractory	MRI
Cranial neuropathy	MRI + contrast
Meningeal disease	MRI + contrast
Spine	
Low back pain	
No neurologic deficits	MRI or CT after >6 weeks
With focal deficits	MRI > CT
Spinal stenosis	MRI or CT
Cervical spondylosis	MRI, CT, CT myelography
Infection	MRI + contrast, CT
Myelopathy	MRI + contrast
Arteriovenous malformation	MRI + contrast, angiography

Abbreviations: CTA, CT angiography; MRA, magnetic resonance angiography; US, ultrasound.

immunologic reactions to contrast agents. A rise in serum creatinine of at least 44 μmol/L (0.5 mg/dL) within 48 hours of contrast administration is often used as a definition of contrast nephropathy, although there is no accepted definition and other causes of acute renal failure must be excluded. The prognosis is usually favorable, with serum creatinine levels returning to baseline within 1–2 weeks. Risk factors for contrast nephropathy include age (>80 years), pre-existing renal disease (serum creatinine exceeding 2 mg/dL), solitary kidney, diabetes mellitus, dehydration, paraproteinemia, concurrent use of nephrotoxic medication or chemotherapeutic agents, and high contrast dose. Patients with diabetes and those with mild renal failure should be well hydrated prior to the administration of contrast agents; careful consideration should be given to alternative imaging techniques such as CT or MRI without contrast, or ultrasound. If contrast must be administered to a patient with known risk factors, the patient should be well hydrated, and a reduction in the dose of contrast should be considered.

X-5. **The answer is C.** *(Chap. 416)* A rare complication, nephrogenic systemic fibrosis (NSF), has occurred in patients with severe renal insufficiency who have been exposed to linear (groups 1 and 3) gadolinium contrast agents. The onset of NSF has been reported between 5 and 75 days following exposure; histologic features include thickened collagen bundles with surrounding clefts, mucin deposition, and increased numbers of fibrocytes and elastic fibers in skin. In addition to dermatologic symptoms, other manifestations include widespread fibrosis of the skeletal muscle, bone, lungs, pleura, pericardium, myocardium, kidney, muscle, bone, testes, and dura. The incidence of NSF in patients with severe renal dysfunction (glomerular filtration rate <30) varies from 0.19 to 4%. Other risk factors for NSF include acute kidney injury, the use of non-macrocyclic agents, and repeated or high-dose exposure to gadolinium.

X-6. **The answer is E.** *(Chap. 416)* While this question is somewhat comical, serious injuries have been caused by attraction of ferromagnetic objects into the magnet, which act as missiles if brought too close to the magnet. Likewise, ferromagnetic implants, such as aneurysm clips, may torque within the magnet, causing damage to vessels and even death. Metallic foreign bodies in the eye have moved and caused intraocular hemorrhage; screening for ocular metallic fragments is indicated in those with a history of metal work or ocular metallic foreign bodies. Implanted cardiac pacemakers are generally a contraindication to MRI because of the risk of induced arrhythmias; however, some newer pacemakers have been shown to be safe. All health care personnel and patients must be screened and educated thoroughly to prevent such disasters because the magnet is always “on.”

X-7. **The answer is C.** *(Chap. 417)* Astrocytes represent half or more of all cells in the central nervous system. Traditionally thought to function as simple interstitial supporting cells that provide scaffolds for neuronal migration and contribute to homeostasis, emerging data indicate far more pleiotropic functions for this cell type. Astrocytes exert profound roles in the life of synapses by secreting factors (such as apolipoprotein E, thrombospondins, and glypicans) that regulate development, maintenance, and pruning of presynaptic and postsynaptic structures. Influenced by local neuronal activity, astrocytes actively phagocytose synapses. Astrocytes also participate in dynamic regulation of vascular tone, in part through astrocyte-astrocyte communication mediated through gap junctions and calcium waves modulated by neuronal activity; support blood-brain barrier and glymphatic integrity through extension of foot process to the vascular structures and expression of aquaporin-4 water channels; and carry out additional metabolic functions essential for the maintenance of neuronal health.

X-8. **The answer is D.** *(Chap. 418)* Age of presentation is an important consideration when an individual presents with a new onset of seizure as certain causes of seizures are more likely to present within certain age ranges, ranging from the neonatal period throughout older adulthood (age >35 years) (Table X-8). In individuals >35 years, the most likely causes of new-onset seizures include alcohol withdrawal, cerebrovascular disease, brain tumor, autoantibodies, Alzheimer’s disease or other neurodegenerative disease, and a range of metabolic disorders. These disorders can include either hyper- or hypoglycemia, uremia, hepatic failure, and a host of electrolyte abnormalities or acid-base disorders. Inherited disorders of ion channels have been implicated in a variety of rare epilepsy syndromes. These genetic disorders typically present in childhood and rarely after the age of 18.

X-9. **The answer is A.** *(Chap. 418)* Overall 70% of children and 60% of adults will be able to successfully discontinue antiepileptic drugs without recurrence of seizures. However, the data regarding the time frame to attempt weaning of antiepileptic drugs are scarce. Once the determination to discontinue antiepileptic drugs has been made, the dosage of medication is typically decreased over a 2- to 3-month period, gradually weaning to off. If a recurrence of seizure were to happen, it is most likely during the first 3 months after discontinuation of therapy. Four factors predict the greatest likelihood of remaining seizure free on discontinuation of antiepileptic drugs: (1) complete control of seizures for 1–5 years; (2) single seizure type—focal or generalized; (3) normal electroencephalogram;

TABLE X-8 Causes of Seizures

Neonates (<1 month)	Perinatal hypoxia and ischemia Intracranial hemorrhage and trauma CNS infection Metabolic disturbances (hypoglycemia, hypocalcemia, hypomagnesemia, pyridoxine deficiency) Drug withdrawal Developmental disorders Genetic disorders
Infants and children (>1 month and <12 years)	Febrile seizures Genetic disorders (metabolic, degenerative, primary epilepsy syndromes) CNS infection Developmental disorders Trauma
Adolescents (12–18 years)	Trauma Genetic disorders Infection Illicit drug use Brain tumor
Young adults (18–35 years)	Trauma Alcohol withdrawal Illicit drug use Brain tumor Autoantibodies
Older adults (>35 years)	Cerebrovascular disease Brain tumor Alcohol withdrawal Metabolic disorders (uremia, hepatic failure, electrolyte abnormalities, hypoglycemia, hyperglycemia) Alzheimer's disease and other degenerative CNS diseases Autoantibodies

Abbreviation: CNS, central nervous system.

and (4) normal neurologic examination, including intelligence. Given that this patient continues to have an abnormal neurologic examination following closed head trauma, he would have a greater likelihood to have a poorer outcome after withdrawal of his seizure medication.

X-10. **The answer is C.** *(Chap. 418)* Status epilepticus is a medical emergency that can result in severe metabolic derangements, hyperthermia, cardiorespiratory collapse, and irreversible neuronal injury. Prompt recognition and appropriate treatment are necessary to prevent long-term sequelae of this neuronal injury. Status epilepticus is defined as continuous seizures or repetitive discrete seizures with impaired consciousness in the interictal period. Status epilepticus has many subtypes with the most common subtype leading to presentation and critical care admission being generalized convulsive status epilepticus (GCSE). The duration of seizure activity that leads to a diagnosis of GCSE is typically defined as 15–30 minutes, but practically if intervention with anticonvulsant medication is required to stop the seizure activity, then one must be concerned about GCSE. Likewise, if a seizure is of sufficient duration to cause significant metabolic or cardiorespiratory consequence, GCSE must be considered. Once GCSE is diagnosed, initial treatment should include basic cardiopulmonary support, including maintaining an appropriate airway, establishing venous access, and obtaining samples of laboratory analysis to identify contributing laboratory abnormalities. It is important to understand that suppression of convulsive activity through the use of paralytic agents does not suppress the epileptic activity in the central nervous system nor does it prevent ongoing neuronal injury and death. Thus, when these agents are used for rapid sequence intubation, the treating team should also continue to treatment for GCSE through appropriate use of IV benzodiazepines initially

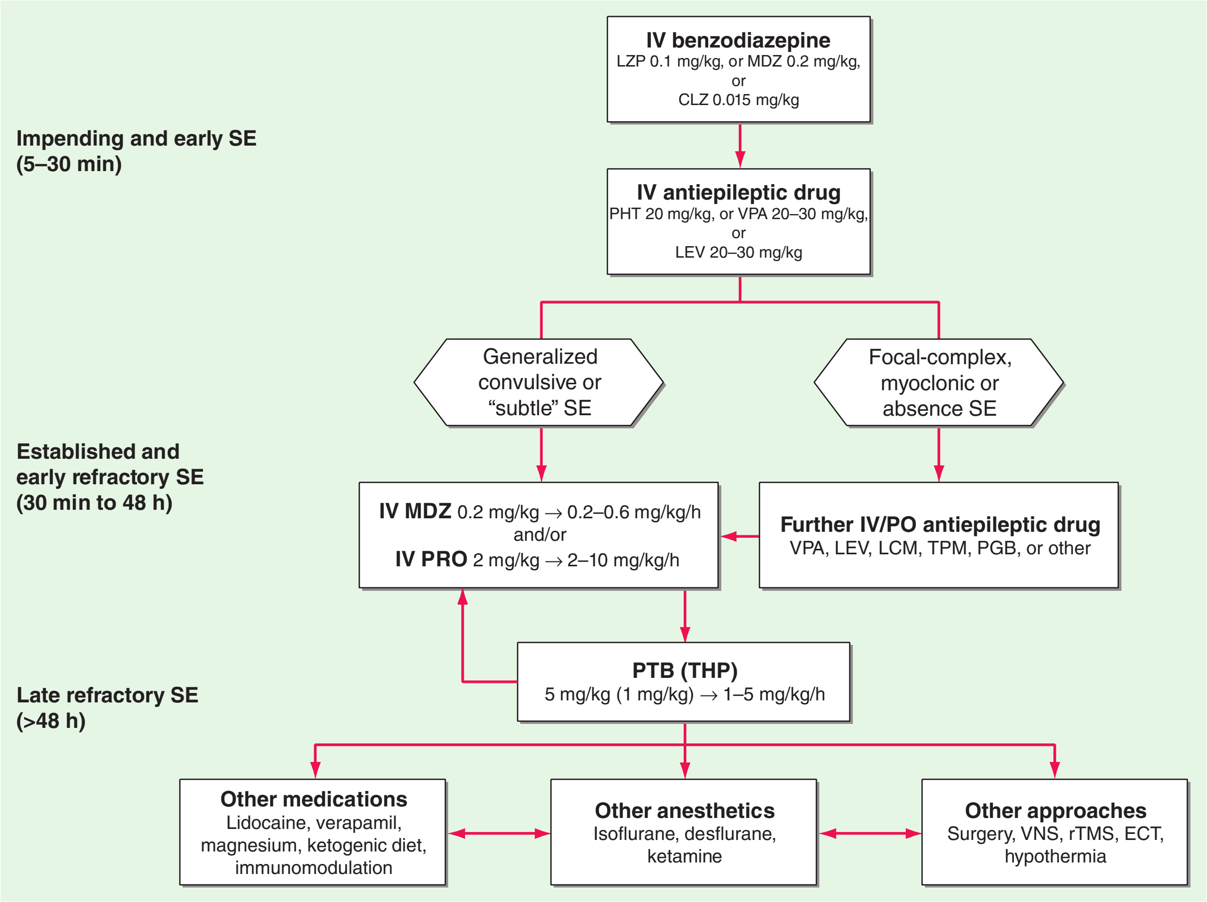

Impending and early SE
(5–30 min)
IV benzodiazepine
LZP 0.1 mg/kg, or MDZ 0.2 mg/kg,
or
CLZ 0.015 mg/kg
IV antiepileptic drug
PHT 20 mg/kg, or VPA 20–30 mg/kg,
or
LEV 20–30 mg/kg
Generalized convulsive or "subtle" SE
Focal-complex, myoclonic or absence SE
Established and early refractory SE
(30 min to 48 h)
IV MDZ 0.2 mg/kg → 0.2–0.6 mg/kg/h
and/or
IV PRO 2 mg/kg → 2–10 mg/kg/h
Further IV/PO antiepileptic drug
VPA, LEV, LCM, TPM, PGB, or other
Late refractory SE
(>48 h)
PTB (THP)
5 mg/kg (1 mg/kg) → 1–5 mg/kg/h
Other medications
Lidocaine, verapamil, magnesium, ketogenic diet, immunomodulation
Other anesthetics
Isoflurane, desflurane, ketamine
Other approaches
Surgery, VNS, rTMS, ECT, hypothermia

FIGURE X-10 *Abbreviations*: CLZ, clonazepam; ECT, electroconvulsive therapy; LCM, lacosamide; LEV, levetiracetam; LZP, lorazepam; MDZ, midazolam; PGB, pregabalin; PHT, phenytoin or fosphenytoin; PRO, propofol; PTB, pentobarbital; rTMS, repetitive transcranial magnetic stimulation; SE, status epilepticus; THP, thiopental; TPM, topiramate; VNS, vagus nerve stimulation; VPA, valproic acid. (Adapted with permission from Rossetti AO, Lowenstein DH: Management of refractory status epilepticus in adults: still more questions than answers. *Lancet Neurol* 10:922, 2011.)

followed by loading doses of either IV phenytoin or fosphenytoin, valproic acid, or levetiracetam (Figure X-10). In many cases, continuous electroencephalogram monitoring may be required to determine when the seizure activity has ceased. If the seizure activity fails to break with these agents, further therapy with propofol or pentobarbital may be required. In more severe cases, inhaled anesthetics may be required. In addition, it is important to treat any underlying infection or metabolic derangements.

X-11. **The answer is C.** *(Chap. 418)* A fundamental principle is that seizures may be either focal or generalized. Focal seizures originate within networks limited to one brain region (note that the term partial seizures is no longer used). Generalized seizures arise within and rapidly engage networks distributed across both cerebral hemispheres. Focal seizures are usually associated with structural abnormalities of the brain. Focal seizure can evolve into generalized seizures. In contrast, generalized seizures may result from cellular, biochemical, or structural abnormalities that have a more widespread distribution.

X-12. **The answer is B.** *(Chap. 418)* Typical absence seizures are characterized by sudden, brief lapses of consciousness without loss of postural control. The seizure usually lasts for only seconds, consciousness returns as suddenly as it was lost, and there is no postictal confusion. Although the brief loss of consciousness may be clinically inapparent or the sole manifestation of the seizure discharge, absence seizures are usually accompanied by subtle, bilateral motor signs such as rapid blinking of the eyelids; chewing movements; or small-amplitude, clonic movements of the hands. Typical absence seizures are associated with a group of genetically determined epilepsies with onset usually in childhood (ages 4–10 years) or early adolescence and are the main seizure type in 15–20% of children with epilepsy. The seizures can occur hundreds of times per day, but the child may be unaware of or unable to convey their existence. Because the clinical signs of the seizures are subtle, especially to parents who may not have had previous experience with seizures, it is not surprising that the first clue to absence epilepsy is often unexplained "daydreaming" and a decline in school performance recognized by a teacher. The electrophysiologic hallmark of typical absence seizures is a generalized, symmetric, 3-Hz spike-and-slow-wave discharge that begins and ends suddenly, superimposed on a normal electroencephalogram (EEG) background. Periods of spike-and-slow-wave discharges lasting more than a few seconds usually correlate with clinical signs, but the EEG often shows many more brief bursts of abnormal cortical activity than were suspected clinically. Hyperventilation tends to provoke these electrographic discharges and even the seizures themselves and is routinely used when recording the EEG.

X-13. **The answer is B.** *(Chap. 419)* The choice to perform a carotid endarterectomy for carotid stenosis depends on many factors, including the degree of stenosis and whether the patient is symptomatic. In general, carotid endarterectomy has been demonstrated to have the greatest benefit in those who are symptomatic and have stenosis ≥70%. In individuals with asymptomatic carotid artery stenosis, the risk of stroke is ~2% per year, and the potential benefits of the procedure may be outweighed by the risks. A more measured approach with risk factor modification may be more prudent. In symptomatic individuals such as this case, several trials have attempted to address the value of carotid endarterectomy. In symptomatic individuals, there is a significant absolute risk reduction of 17% favoring surgery. In the symptomatic patient, the annual risk of stroke is ~13%. A recent meta-analysis showed that carotid endarterectomy is most beneficial when performed within 2 weeks of symptom onset, and it has greater benefits in men and those ≥ 75 years. However, the procedure should be performed only in institutions with familiarity with the procedure. The benefit of the procedure is questionable for any surgeon whose perioperative stroke rate is ≥6%.

X-14. **The answer is B.** *(Chaps. 419 and 420)* Once the clinical diagnosis of stroke is made, a brain imaging study is necessary to determine whether the cause of stroke is ischemia or hemorrhage. CT imaging of the brain is the standard imaging modality to detect the presence or absence of intracranial hemorrhage. If the stroke is ischemic, administration of recombinant tissue plasminogen activator or endovascular mechanical thrombectomy may be beneficial in restoring cerebral perfusion (Figure X-14). Medical management to reduce the risk of complications becomes the next priority, followed by plans for secondary prevention. For ischemic stroke, several strategies can reduce the risk of subsequent stroke in all patients, while other strategies are effective for patients with specific causes of stroke such as cardiac embolus and carotid atherosclerosis.

X-15. **The answer is E.** *(Chap. 419)* Metabolic encephalopathies typically produce fluctuating mental status changes without focal neurologic findings. However, in the setting of prior stroke or brain injury, a patient with fever or sepsis may manifest a recurrent hemiparesis, which clears rapidly when the infection is treated. The metabolic process serves to "unmask" a prior deficit.

X-16. **The answer is B.** *(Chap. 420)* The National Institute of Neurological Disorders and Stroke (NINDS) rtPA Stroke Study showed a clear benefit for IV recombinant tissue plasminogen activator (rtPA) in selected patients with acute stroke. The NINDS study used IV rtPA (0.9 mg/kg to a 90-mg maximum; 10% as a bolus, then the remainder over 60 minutes) versus placebo in ischemic stroke within 3 hours of onset. One-half of the patients were treated within 90 minutes. Symptomatic intracranial hemorrhage occurred in 6.4% of patients on rtPA and 0.6% on placebo. In the rTPA group, there was a significant 12% absolute increase in the number of patients with only minimal disability (32% on placebo and 44% on rtPA) and a nonsignificant 4% reduction in mortality (21% on placebo and 17% on rtPA). Thus, despite an increased incidence of symptomatic intracranial hemorrhage, treatment with IV rtPA within 3 hours of the onset of ischemic stroke improved clinical outcome. Three subsequent trials of IV rtPA did not confirm this benefit, perhaps because of the dose of rtPA used, the timing of its delivery, and small sample size. When data from all randomized IV rtPA trials were combined, however, efficacy was confirmed

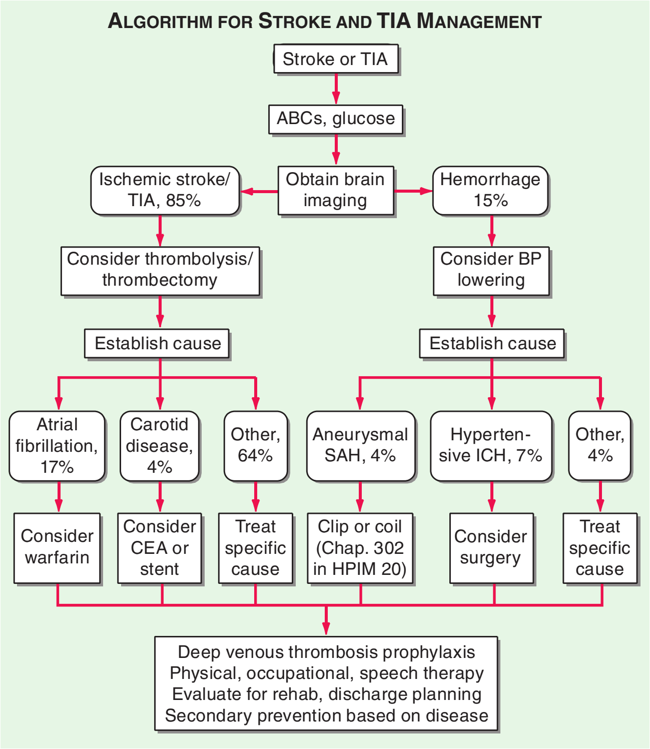

Algorithm for Stroke and TIA Management
Stroke or TIA
ABCs, glucose
Obtain brain imaging
Ischemic stroke/ TIA, 85%
Hemorrhage 15%
Consider thrombolysis/ thrombectomy
Consider BP lowering
Establish cause
Establish cause
Atrial fibrillation, 17%
Carotid disease, 4%
Other, 64%
Aneurysmal SAH, 4%
Hypertensive ICH, 7%
Other, 4%
Consider warfarin
Consider CEA or stent
Treat specific cause
Clip or coil (Chap. 302 in HPIM 20)
Consider surgery
Treat specific cause
Deep venous thrombosis prophylaxis
Physical, occupational, speech therapy
Evaluate for rehab, discharge planning
Secondary prevention based on disease

FIGURE X-14 *Rounded boxes* are diagnoses; *rectangles* are interventions. Numbers are percentages of stroke overall. *Abbreviations*: ABCs, airway, breathing, circulation; BP, blood pressure; CEA, carotid endarterectomy; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; TIA, transient ischemic attack.

in the less than 3-hour time window, and efficacy likely extended to 4.5 hours and possibly to 6 hours. Based on these combined results, the European Cooperative Acute Stroke Study III explored the safety and efficacy of rtPA in the 3- to 4.5-hour time window. Unlike the NINDS study, patients aged >80 years and diabetic patients with a previous stroke were excluded. In this 821-patient randomized study, efficacy was again confirmed, although the treatment effect was less robust than in the 0- to 3-hour time window. In the rtPA group, 52.4% of patients achieved a good outcome at 90 days, compared with 45.2% of the placebo group (odds ratio [OR] 1.34, $p = 0.04$). The symptomatic intracranial hemorrhage rate was 2.4% in the rtPA group and 0.2% in the placebo group ($p = 0.008$). Based on these data, rtPA is approved in the 3- to 4.5-hour window in Europe and Canada, but it is still only approved for 0–3 hours in the United States. If thrombolysis is considered, an assessment for contraindications is required prior to administration (Table X-16). In this patient, the sustained hypertension is a contraindication.

X-17. **The answer is B.** *(Chap. 420)* The relationship of various factors to the risk of atherosclerosis are well described. Older age, diabetes mellitus, hypertension, tobacco smoking, abnormal blood cholesterol (particularly, low high-density lipoprotein [HDL] and/or elevated low-density lipoprotein [LDL]), and other factors are either proven or probable risk factors for ischemic stroke, largely by their link to atherosclerosis. Risk of stroke is much greater in those with prior stroke or transient ischemic attack. Many cardiac conditions predispose to stroke, including atrial fibrillation and recent myocardial infarction. Oral contraceptives and hormone replacement therapy increase stroke risk, and although rare, certain inherited and acquired hypercoagulable states predispose to stroke. Hypertension is the most significant of the risk factors; in general, all hypertension should be treated to a target of <130/80. Recent data (the Systolic Blood Pressure Intervention Trial) suggest that lowering systolic blood pressure <120 reduces stroke and heart attack by 43% compared with systolic blood pressure <140, without an increased risk of syncope or falls. The presence of known cerebrovascular disease is not a contraindication to treatment aimed at achieving normotension.

TABLE X-16 Administration of IV Recombinant Tissue Plasminogen Activator (rtPA) for Acute Ischemic Stroke (AIS)[a]

Indication	Contraindication
Clinical diagnosis of stroke	Sustained BP >185/110 despite treatment
Onset of symptoms to time of drug administration ≤4.5 h[b]	Bleeding diathesis
CT scan showing no hemorrhage or edema of >1/3 of the MCA territory	Recent head injury or intracerebral hemorrhage
Age 18 ≥ years	Major surgery in preceding 14 days
	Gastrointestinal bleeding in preceding 21 days
	Recent myocardial infarction

Administration of rtPA
IV access with two peripheral IV lines (avoid arterial or central line placement)
Review eligibility for rtPA
Administer 0.9 mg/kg IV (maximum 90 mg) IV as 10% of total dose by bolus, followed by remainder of total dose over 1 h[c]
Frequent cuff blood pressure monitoring
No other antithrombotic treatment for 24 h
For decline in neurologic status or uncontrolled BP, stop infusion, give cryoprecipitate, and reimage brain emergently
Avoid urethral catheterization for ≥2 h

[a] See Activase (tissue plasminogen activator) package insert for complete list of contraindications and dosing.
[b] Depending on the country, IV rtPA may be approved for up to 4.5 h with additional restrictions.
[c] A dose of 0.6 mg/kg is commonly used in Asia (Japan and China) based on randomized data indicating less hemorrhage and similar efficacy using this lower dose.
Abbreviations: BP, blood pressure; MCA, middle cerebral artery.

X-18. **The answer is E.** *(Chap. 420)* Aspirin is the most widely studied antiplatelet agent. Aspirin acetylates platelet cyclooxygenase, which irreversibly inhibits the formation in platelets of thromboxane A_2, a platelet aggregating and vasoconstricting prostaglandin. This effect is permanent and lasts for the usual 8-day life of the platelet. Paradoxically, aspirin also inhibits the formation in endothelial cells of prostacyclin, an antiaggregating and vasodilating prostaglandin. This effect is transient. As soon as aspirin is cleared from the blood, the nucleated endothelial cells again produce prostacyclin. Aspirin in low doses given once daily inhibits the production of thromboxane A_2 in platelets without substantially inhibiting prostacyclin formation. Higher doses of aspirin have not been proven to be more effective than lower doses.

X-19. **The answer is C.** *(Chap. 420)* This patient has atrial fibrillation with an elevated CHA_2DS_2-VASc score. CHA_2DS_2-VASc score is calculated as follows: 1 point for *C*ongestive heart failure, 1 point for *H*ypertension, 2 points for *A*ge ≥ 75 years, 1 point for *D*iabetes mellitus, 2 points for *S*troke or transient ischemic attack (TIA), 1 point for *V*ascular disease (prior myocardial infarction, peripheral vascular disease, or aortic plaque), 1 point for *A*ge 65–74, and 1 point for female *S*ex category. The sum of the points is the total CHA_2DS_2-VASc score. This patient gets a point for congestive heart failure and a point for diabetes mellitus. Recommendations for anticoagulation in atrial fibrillation are as shown in Table X-19. Several trials have shown that anticoagulation (international normalized ratio range [INR] 2–3) in patients with chronic nonvalvular (nonrheumatic) atrial fibrillation (NVAF) prevents cerebral embolism and stroke and is safe. For primary prevention and for patients who have experienced stroke or TIA, anticoagulation with a vitamin K antagonist (VKA) reduces the risk by about 67%, which clearly outweighs the 1–3% risk per year of a major bleeding complication. VKAs are difficult to dose, their effects vary with dietary intake of vitamin K, and they require frequent blood monitoring of the PTT/INR. Several newer oral anticoagulants have recently been shown to be more convenient and efficacious for stroke prevention in NVAF. A randomized trial compared the oral thrombin inhibitor dabigatran with VKAs in a noninferiority trial to prevent stroke or systemic embolization in NVAF. Two doses of dabigatran were used: 110 mg/d and 150 mg/d. Both dose tiers of dabigatran were noninferior to VKAs in preventing second stroke and systemic embolization, and the higher dose tier was superior (relative risk 0.66; 95% confidence interval 0.53–0.82; p <0.001) and the rate of major bleeding was lower in the lower dose tier of dabigatran compared with VKAs. Dabigatran requires no blood monitoring to

TABLE X-19 Recommendations on Chronic Use of Antithrombotics for Various Cardiac Conditions

Condition	Recommendation
Nonvalvular atrial fibrillation	Calculate CHA_2DS_2-VASc score[a]
• CHA_2DS_2-VASc score of 0	Aspirin or no antithrombotic
• CHA_2DS_2-VASc score of 1	Aspirin or OAC
• CHA_2DS_2-VASc score of 2 or greater	OAC
Rheumatic mitral valve disease	
• With atrial fibrillation, previous embolization, or atrial appendage thrombus, or left atrial diameter >55 mm	OAC
• Embolization or appendage clot despite OAC	OAC plus aspirin
Mitral valve prolapse	
• Asymptomatic	No therapy
• With otherwise cryptogenic stroke or TIA	Aspirin
• Atrial fibrillation	OAC
Mitral annular calcification	
• Without atrial fibrillation but systemic embolization, or otherwise cryptogenic stroke or TIA	Aspirin
• Recurrent embolization despite aspirin	OAC
• With atrial fibrillation	OAC
Aortic valve calcification	
• Asymptomatic	No therapy
• Otherwise cryptogenic stroke or TIA	Aspirin
Aortic arch mobile atheroma	
• Otherwise cryptogenic stroke or TIA	Aspirin or OAC
Patent foramen ovale	
• Otherwise cryptogenic ischemic stroke or TIA	Aspirin or closure with device
• Indication for OAC (deep-venous thrombosis or hypercoagulable state)	OAC
Mechanical heart value	
• Aortic position, bi-leaflet or Medtronic Hall tilting disk with normal left atrial size and sinus rhythm	VKA INR 2.5, range 2–3
• Mitral position tilting disk or bi-leaflet valve	VKA INR 3.0, range 2.5–3.5
• Mitral or aortic position, anterior-apical myocardial infarct or left atrial enlargement	VKA INR 3.0, range 2.5–3.5
• Mitral or aortic position, with atrial fibrillation, or hypercoagulable state, or low ejection fraction, or atherosclerotic vascular disease	Aspirin plus VKA INR 3.0, range 2.5–3.5
• Systemic embolization despite target INR	Add aspirin and/or increase INR: prior target was 2.5 increase to 3.0, range 2.5–3.5; prior target was 3.0 increase to 3.5, range 3–4
Bioprosthetic valve	
• No other indication for VKA therapy	Aspirin
• Infective endocarditis	Avoid antithrombotic agents
Nonbacterial thrombotic endocarditis	
• With systemic embolization	Full-dose unfractionated heparin or SC LMWH

[a] CHA_2DS_2-VASc score is calculated as follows: 1 point for *C*ongestive heart failure, 1 point for *H*ypertension, 2 points for *A*ge ≥75 years, 1 point for *D*iabetes mellitus, 2 points for *S*troke or TIA, 1 point for *V*ascular disease (prior myocardial infraction, peripheral vascular disease, or aortic plaque), 1 point for *A*ge 65–74 years, 1 point for female *S*ex category; sum of points is the total CHA_2DS_2-VASc score.
Note: Dose of aspirin is 50–325 mg/d; target INR for OAC is between 2 and 3 unless otherwise specified.
Abbreviations: INR, international normalized ratio; LMWH, low-molecular-weight heparin; OAC, oral anticoagulant (VKA, thrombin inhibitor, or oral factor Xa inhibitors); TIA, transient ischemic attack; VKA, vitamin K antagonist.
Source: Data from Singer DE et al: *Chest* 133:546S, 2008; Salem DN et al: *Chest* 133:593S, 2008; January CT et al: *JACC* 64:2246, 2014.

titrate the dose, and its effect is independent of oral intake of vitamin K. Newer oral factor Xa inhibitors have also been found to be equivalent or safer and more effective than VKAs in NVAF stroke prevention. In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial, patients were randomized between apixaban, 5 mg twice daily, and dose-adjusted warfarin (INR 2–3). The combined end point of ischemic or hemorrhagic stroke or system embolism occurred in 1.27% of patients in the apixaban group and in 1.6% in the warfarin group (p <0.001 for noninferiority and p <0.01 for superiority). Major bleeding was 1% less, favoring apixaban (p <0.001).

X-20. **The answer is A.** *(Chap. 420)* Aspirin is the only antiplatelet agent that has been proven to be effective for the acute treatment of ischemic stroke; there are several antiplatelet agents proven for the secondary prevention of stroke. Two large trials, the International Stroke Trial (IST) and the Chinese Acute Stroke Trial (CAST), found that the use of aspirin within 48 hours of stroke onset reduced both stroke recurrence risk and mortality minimally. Among 19,435 patients in IST, those allocated to aspirin, 300 mg/d, had slightly fewer deaths within 14 days (9.0% vs 9.4%), significantly fewer recurrent ischemic strokes (2.8% vs 3.9%), no excess of hemorrhagic strokes (0.9% vs 0.8%), and a trend toward a reduction in death or dependence at 6 months (61.2% vs 63.5%). In CAST, 21,106 patients with ischemic stroke received 160 mg/d of aspirin or a placebo for up to 4 weeks. There were very small reductions in the aspirin group in early mortality (3.3% vs 3.9%), recurrent ischemic strokes (1.6% vs 2.1%), and dependency at discharge or death (30.5% vs 31.6%). These trials demonstrate that the use of aspirin in the treatment of acute ischemic stroke is safe and produces a small net benefit. For every 1000 acute strokes treated with aspirin, about 9 deaths or nonfatal stroke recurrences will be prevented in the first few weeks and ~13 fewer patients will be dead or dependent at 6 months.

X-21. **The answer is C.** *(Chap. 421)* This patient has alteration in mental status and is not protecting his airway. Close attention should be paid to airway management because a reduction in the level of consciousness is common and often progressive in patients with intracranial hemorrhage. Despite adequate oxygenation at this moment, this patient requires emergent intubation after which therapy directed at alleviating his intracranial hemorrhage can proceed.

X-22. **The answer is B.** *(Chap. 421)* In pontine hemorrhages, deep coma with quadriplegia often occurs over a few minutes. Typically, there is prominent decerebrate rigidity and "pinpoint" (1 mm) pupils that react to light. There is impairment of reflex horizontal eye movements evoked by head turning (doll's-head or oculocephalic maneuver) or by irrigation of the ears with ice water. Hyperpnea, severe hypertension, and hyperhidrosis are common. Most patients with deep coma from pontine hemorrhage ultimately die, or develop a locked-in state, but small hemorrhages are compatible with survival and significant recovery.

X-23. **The answer is E.** *(Chap. 421)* Intracranial hemorrhage accounts for ~10% of all strokes, and about 35–45% of patients die within the first month. Incidence rates are particularly high in Asians and blacks. Hypertension, coagulopathy, sympathomimetic drugs (cocaine, methamphetamine), and cerebral amyloid angiopathy cause most of these hemorrhages. Advanced age, heavy alcohol, and low-dose aspirin use in those without symptomatic cardiovascular disease increase the risk. Cocaine and methamphetamine use is one of the most important causes in the young. In this patient with no prior medical history, a urine drug toxicology screen is indicated.

X-24. **The answer is C.** *(Chap. 422)* The patient describes a typical history for migraine headaches, the second most common cause of headache and most common cause of headache-related disability worldwide. Migraine affects approximately 15% of women and 6% of men in any given year. Diagnostic criteria for migraine have been simplified recently. To diagnose migraine, an individual should complain of repeated attacks of headache lasting from 4 to 72 hours, with a normal physical examination, and no other clear cause. The headache should be associated with two of the four following features: unilateral pain, throbbing pain, aggravation by movement, or moderate to severe intensity. In addition, the individual should complain of either nausea/vomiting or phonophobia and photophobia. Most individuals with migraine headaches can identify triggers associated with an attack. Common triggers include lack of sleep or excessive sleep, stress, hormonal fluctuations, alcohol, or barometric pressures changes. The pathophysiology that underlies migraine is increasingly understood as a dysfunction of the monoaminergic sensory control systems located in the brainstem and hypothalamus. Activation of cells in the trigeminal nucleus leads to release of vasoactive neuropeptides at vascular terminations of the trigeminal nerve and within the trigeminal nucleus. These neurons also project centrally, crossing the midline, to project to ventrobasal and posterior nuclei of the posterior thalamus. The primary vasoactive peptide that has been implicated is calcitonin gene-related peptide (CGRP). A new class of medication called gepants is being developed to act as an antagonist at the CGRP receptor and has been demonstrated to be effective against migraine in early clinical trials. The most common medications used for acute relief of severe migraine pain are the triptans, potent agonists of the 5-hydroxytryptamine (serotonin) receptor, implicating serotonin in pathogenesis of migraine as well. It is thought that serotonin is necessary for nociceptive signaling in the trigeminovascular system, and that triptans arrest this pathway. Finally, dopamine may also play a role in pathogenesis of migraine as migraine symptoms can be induced by dopamine stimulation, and individuals with migraine have been demonstrated to have hypersensitivity to dopamine agonists at doses that do not affect non–migraine-affected persons. In the past, the "vascular theory" of migraine was frequently espoused with the cause of migraine thought to be related to abnormal cerebral vasodilation. This theory has been discounted as the pathogenesis is more widely understood.

X-25. **The answer is A.** *(Chap. 422)* Cluster headache is a rare disorder affecting only about 0.1% of the population. This episodic headache disorder is characterized by severe unilateral headache of relatively short-duration that occurs over 8–10 weeks a year, followed by prolonged pain-free intervals that average a little less than a year. As opposed to migraine, men are more likely to have cluster headache, but cluster headache does share some features common to migraine including the unilateral nature of the pain and the stabbing or throbbing characteristics of the pain. In addition, a patient with cluster headache may also complain of nausea, photophobia, or phonophobia during the attack. In contrast, however, patients with cluster headache tend to move about during an attack. A cluster headache is accompanied by ipsilateral symptoms of cranial parasympathetic activation including lacrimation, rhinorrhea or nasal congestion, and ptosis. The headache in cluster headache is explosive in onset and associated with intense pain. During a cluster attack, the headaches can occur as infrequently as every other day to several times daily. The duration of pain is variable between 15 and 180 minutes. Cluster headache falls within a category of trigeminal autonomic cephalgias along with paroxysmal hemicranias, and short-lasting unilateral neuralgiform headaches with conjunctival injection and tearing (SUNCT) or short-lasting unilateral neuralgiform headaches attacks with cranial autonomic symptoms (SUNA). It can be differentiated from these based on historical factors. In paroxysmal hemicrania, the attacks are more frequent, occurring between 1 and 20 times per day and last 2–30 minutes. Males and females are equally affected. SUNCT/SUNA are rare disorders that are easily distinguished from cluster headache. A patient with one of these disorders will have 3–200 episodes of unilateral pain daily but the duration is less than 5 minutes. Migraine headache is a unilateral throbbing headache associated with phonophobia, photophobia, and nausea and vomiting. It is more common in women than men, and is not associated with the symptoms of tearing or nasal congestion. Tension headache is the most common cause of headache and does not typically cause debilitating pain. The pain of a tension headache is described as band-like.

X-26. **The answer is E.** *(Chap. 422)* A useful clinical approach is to diagnose tension-type headache (TTH) in patients whose headaches are completely without accompanying features such as nausea, vomiting, photophobia, phonophobia, osmophobia, throbbing, and aggravation with movement. Such an approach neatly separates migraine, which has one or more of these features and is the main differential diagnosis, from TTH.

X-27. **The answer is E.** *(Chap. 422)* The pain of tension-type headaches (TTHs) can generally be managed with simple analgesics such as acetaminophen, aspirin, or nonsteroidal anti-inflammatory drugs. Behavioral approaches including relaxation can also be effective.

Clinical studies have demonstrated that triptans in pure TTH are not helpful, although triptans are effective in TTH when the patient also has migraine. For chronic TTH, amitriptyline is the only proven treatment; other tricyclics, selective serotonin reuptake inhibitors, and the benzodiazepines have not been shown to be effective. There is no evidence for the efficacy of acupuncture. Placebo-controlled trials of onabotulinum toxin type A in chronic TTH were negative.

X-28. **The answer is C.** *(Chap. 423)* Significant memory loss affects about 10% of all individuals greater than 70 years of age, and in more than half, the cause is Alzheimer's disease (AD). AD is the leading cause of dementia and typically presents as slowly progressive memory loss that develops over many years. Early in the disease, the memory loss often goes unrecognized or is attributed to the effects of aging. Memory deficits are typically not noticeable to the patient or spouse until the deficits fall below 1.5 standard deviations below normal on standardized memory tests. When this occurs, the term mild cognitive impairment (MCI) is applied. Among those diagnosed with MCI, about 50% progress to AD over 4 years. Many neurologists have begun to replace MCI with the term "early symptomatic AD." As the cognitive disease progresses, patients will lose their ability to maintain their higher order daily activities such as driving, shopping, housekeeping, and maintaining finances. Most patients are aware of the loss of these abilities in early stages of the disease. In middle stages of the disease, the patient loses the ability to work and is easily lost and confused. Language is increasingly impaired in both comprehension and fluency. Motor apraxia also becomes noticeable. In advanced stages of the disease, patients may remain ambulatory, but often wander aimlessly. There is a loss of judgment and reasoning. The patient may have delusions and may not recognize caregivers. The pathologic hallmark of AD is the presence of neuritic plaques containing amyloid beta and neurofibrillary tangles (option C) containing hyperphosphorylated tau filament. The earliest and most severe degeneration is seen in the medial temporal lobe, lateral temporal cortex, and nuclear basalis of Meynert. Amyloid deposition in cerebral blood vessels (option A) can be seen in AD, but it is not the pathologic hallmark of AD. It is also seen in a condition called cerebral amyloid angiopathy, which predisposes individuals to cerebral hemorrhage. Frontotemporal lobar degeneration spectrum disorder is a heterogeneous group of disorders including Pick disease, progressive supranuclear palsy, and corticobasal syndrome that share a common gross pathologic hallmark of focal atrophy of the frontal, insular, and/or temporal cortex (option B) with a concomitant loss of serotonergic innervation in many patients. Lewy bodies are intracytoplasmic inclusions that stain positive with periodic acid–Schiff and ubiquitin (option D) that are found throughout specific brainstem nuclei, substantia nigra, amygdala, cingulate gyrus, and neocortex. Lewy bodies are seen in dementia syndromes with parkinsonian features.

X-29. **The answer is E.** *(Chap. 423)* Mild cognitive impairment (MCI) refers to a condition of impaired memory that is 1.5 standard deviations below normal on standardized memory tests. Over 4 years, about 50% of individuals with MCI will progress to Alzheimer's disease (AD). However, no treatment currently has been demonstrated to slow the decline in memory or delay the progression to AD. Donepezil, rivastigmine, and galantamine are U.S. Food and Drug Administration-approved anticholinesterase inhibitors that are approved for use in patients diagnosed with AD. Memantine is also approved for use in moderate to severe AD and blocks N-methyl-D-aspartate glutamate receptors. These medications have modest effects on caregiver ratings of patient functioning and a slight decrease in rate of decline in cognitive test scores over periods of up to 3 years. However, these medications have significant side effects including nausea, diarrhea, altered sleep with vivid dreams, and muscle cramps. Interventions that have been attempted and failed to show benefit have included hormone replacement therapy in post-menopausal women and ginkgo biloba. Many potential therapies are being investigated to ascertain benefit including vaccination against amyloid beta and statin use in early AD. Despite the popularity in the media, "brain training" has not been shown to slow decline in cognitive function.

X-30. **The answer is C.** *(Chaps. 423 and 424)* Frontotemporal dementia (FTD) refers to a group of clinical syndromes that demonstrate frontotemporal lobe degeneration on pathologic examination. FTD typically presents in the fifth to seventh decades of life and is nearly as predominant as Alzheimer's disease in this age group. Three distinct clinical syndromes are described: behavioral variant FTD, semantic primary progressive aphasia, and nonfluent/agrammatic primary progressive aphasia. These syndromes have clinical and MRI findings that allow the clinician to determine the primary diagnosis, although patients may evolve to have prominent features of another syndrome. This patient would have the behavioral variant FTD, the most common of the FTD syndromes. Individuals with behavioral variant FTD demonstrate social and emotional dysfunction with a variety of symptoms including apathy, disinhibition, compulsivity, loss of empathy, and overeating. In addition, there are typically deficits in executive control. Upper motor neuron disease is often seen as well. The MRI shows atrophy of anterior cingulate and frontoinsular areas. In the semantic primary progressive aphasia variant of FTD, patients slowly lose the ability to decode word, object, person-specific, and emotion meaning, and the MRI shows prominent atrophy in the temporopolar area, greater on the left. The nonfluent/agrammatic primary progressive aphasia variant of FTD demonstrates profound inability to produce words and motor speech impairment. The MRI shows dominant frontal opercular and dorsal insula degeneration.

X-31. **The answer is C.** *(Chap. 423)* This patient likely has normal pressure hydrocephalus (NPH), a syndrome characterized by a clinical triad including an abnormal gait (ataxic or apractic), dementia (usually mild to moderate, with an emphasis on executive impairment), and urinary urgency or incontinence. NPH is a relatively uncommon but treatable dementia syndrome. The clinical, physiologic, and neuroimaging characteristics of NPH must be carefully distinguished from those of other dementias associated with gait impairment. Numerous attempts to improve NPH diagnosis with various special studies and predict the success of ventricular shunting have been undertaken. These tests include radionuclide cisternography (showing a delay in cerebrospinal fluid [CSF] absorption over the convexity) and various efforts to monitor and alter CSF flow dynamics, including a constant-pressure infusion test. None has proven to be specific or consistently useful. A transient improvement in gait or cognition may follow lumbar puncture (or serial punctures) with removal of 30–50 mL of CSF, but this finding also has not proved to be consistently predictive of post-shunt improvement. Perhaps the most reliable strategy is a period of close inpatient evaluation before, during, and after lumbar CSF drainage. Three percent to fifty percent of patients identified by careful diagnosis as having NPH will improve with ventricular shunting. Gait may improve more than cognition, but many reported failures to improve cognitively may have resulted from comorbid Alzheimer's disease. Short-lasting improvement is common. Patients should be carefully selected for shunting, because subdural hematoma, infection, and shunt failure are known complications and can be a cause for early nursing home placement in an elderly patient with previously mild dementia.

X-32. **The answer is E.** *(Chap. 424)* This patient's symptoms and MRI findings are consistent with the diagnosis of frontotemporal dementia (FTD). FTD refers to a group of clinical syndromes united by their links to underlying frontotemporal lobar degeneration pathology. Early studies suggested that FTD may be more common in men than women; however, more recent reports cast doubt on this finding. Although a family history of dementia is common, autosomal dominant inheritance is seen in only 10–20% of all FTD cases. Treatment is symptomatic, and there are currently no therapies known to slow progression or improve symptoms. Many of the behaviors that may accompany FTD, such as depression, hyperorality, compulsions, and irritability, can be ameliorated with antidepressants, especially selective serotonin reuptake inhibitor. Drugs with significant anticholinergic properties, such as trazadone, may worsen the dementia. Because FTD is often accompanied by parkinsonism, antipsychotics, which can exacerbate this problem, must be used with caution. Memantine, an N-methyl-D-aspartate receptor antagonist, is used to treat the symptoms of Alzheimer's disease.

X-33. **The answer is A.** *(Chap. 425)* Age remains the strongest risk factor for cerebrovascular disease (CVD) and stroke in the United States. By the age of 70, 70% of the population has white matter disease and lesions on neuroimaging, with small infarcts (lacunar infarcts) found in 11–24% of the population. In addition to genetic predisposition, risk factors that also directly contribute to CVD include chronic hypertension, hyperlipidemia, diabetes, and smoking. Cardiac disease, such as atrial fibrillation or heart failure, can also cause cognitive impairment via embolic infarcts and hypoxemia due to inadequate cerebral blood flow.

X-34. **The answer is E.** *(Chap. 425)* Vascular Dementia (VaD) is strongly associated with hemorrhagic and ischemic strokes, with an estimated one-third of stroke survivors affected by post-stroke dementia or cognitive impairment. Hemorrhages, including subdural, intracerebral, and subarachnoid bleeds, account for roughly 20% of all strokes. The disruption of cerebral networks caused by hemorrhage depends to a certain extent on size and location. Subarachnoid hemorrhage has a more intricate relation with cognitive deficits. Ischemic strokes compose 80% of all strokes. Large-vessel and small-vessel disease (SVD) can lead to dementia, although the mechanisms and clinical presentation vary. In a cross-sectional study of 706 VaD cases, large vessel disease, often referred to as multi-infarct dementia, made up roughly 18% of all cases. Neurobehavioral symptoms vary as a function of cerebral lesion size and location, and it can include aphasia, apraxia, agnosia, and inattention syndromes. Some ambiguity between lesion location and cognitive symptoms continues to persist. This may be a result of the interconnected nature of cognitive, behavioral functional, and structural networks of the brain, as well as the remote consequences of cerebral inflammation and blood-brain barrier disruption caused by strokes. Of all cerebrovascular disease subtypes, chronic cerebral SVD shows the strongest association with cognitive impairment. SVD accounts for 36–67% of all VaDs.

X-35. **The answer is C.** *(Chap. 425)* Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a genetic disorder linked to a mutation in the NOTCH3 gene on chromosome 19. CADASIL presents as small-vessel strokes, progressive dementia, and extensive white matter disease often beginning in mid-adult life. Through altered extracellular molecular signaling pathways and protein elimination failure and accumulation, pericytes and endothelia of small vessels are involved. CADASIL may offer a unique opportunity to study "pure" vascular dementia, as individuals diagnosed with CADASIL tend to display cognitive decline at an early age, when the likelihood of comorbid neurodegenerative diseases is lower. Dystrophin mutations lead to muscular dystrophy. Titin mutations can lead to cardiomyopathy. Transthyretin mutations can lead to familial amyloidosis. *CFTR* mutations are implicated in cystic fibrosis.

X-36. **The answer is C.** *(Chap. 426)* The dementia with Lewy bodies (DLB) syndrome is characterized by visual hallucinations, parkinsonism, fluctuating alertness, neuroleptic sensitivity, rapid eye movement sleep behavior disorder (RBD), and often hyposmia and excessive daytime sleepiness. Delusions related to persecution, invasion, and person or place identity (reduplicative paramnesia) are common. When orthostatic hypotension is present, DLB must be distinguished from multiple system atrophy with parkinsonism (MSA-P). Recurrent, disabling syncope early in the course, accompanied by laryngeal spasms and anterocollis, suggest MSA-P. In DLB, orthostasis can appear early but rarely becomes disabling until well into the course, when neuropsychiatric symptoms and cognitive dysfunction are well established. Patients with DLB and Parkinson disease dementia are highly sensitive to metabolic perturbations, and in some patients the first manifestation of illness is a delirium, often precipitated by an infection, new medicine, or other systemic disturbance. A hallucinatory delirium induced by L-dopa, prescribed for parkinsonian symptoms attributed to Parkinson disease, may likewise provide the initial clue to a DLB diagnosis. Due to the frequent comorbidity with Alzheimer's disease and the cholinergic deficit in DLB, cholinesterase inhibitors often provide significant benefit, reducing hallucinosis, stabilizing delusional symptoms, and even helping with RBD in some patients. Exercise programs maximize motor function and protect against fall-related injury. Antidepressants are often necessary. Atypical antipsychotics may be required for psychosis but can worsen extrapyramidal syndromes, even at low doses, and should be used cautiously, given the side effects, including an increased risk of death.

X-37. **The answer is A.** *(Chap. 427)* Parkinson disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease, affecting approximately 1 million individuals in the United States. PD affects men and women equally with a typical age of symptom onset around age 60. The frequency of PD increases with age, but it can present as early as the third decade of life. Most cases of PD occur sporadically, although genetic factors play a role in some individuals. These individuals are more likely to present at a younger age. There is no single gene found to be associated with PD. The most likely genes to be altered in PD patients include *α-synuclein*, *PINK1/Parkin*, and *LRRK2*, but many others have been identified. Other epidemiologic risk factors for PD include exposure to pesticides, rural living, and drinking well water. Cigarette smoking and caffeine are associated with reduced risk of PD. Pathologically, the characteristic finding in PD is degeneration of the dopaminergic neurons in the substantia nigra pars compacta. Lewy bodies, which are intracytoplasmic inclusions containing primarily α-synuclein, may also be seen.

X-38. **The answer is E.** *(Chap. 427)* This patient exhibits classic features of Parkinson disease (PD), a diagnosis made on the basis of clinical presentation. Historically, PD could be diagnosed if the patient had two of three of the following: bradykinesia, tremor, and rigidity. However, given the significant overlap of these symptoms with atypical or secondary Parkinson syndrome, the diagnosis of PD was incorrect in about 24% of cases (Table X-38). More recently, it has been determined that a more predictive trio of features is resting tremor, asymmetry, and positive response to levodopa. Imaging of the brain may show reduced uptake of striatal dopaminergic markers in the posterior putamen with sparing of the caudate nuclear on positron emission tomography or single-photon emission CT imaging. However, imaging is not required for a diagnosis of PD and is typically only performed under research settings or if there are features that would cause one to suspect an atypical Parkinson syndrome. This patient does not have features that would lead one to suspect atypical parkinsonism. He also has no medications or other clinical conditions that would lead to secondary parkinsonism. The most common causes of secondary parkinsonism include stroke, tumor, infection, exposure to toxins such as carbon

TABLE X-38 **Features Suggesting an Atypical or Secondary Cause of Parkinsonism**

Symptoms/Signs	Alternative Diagnosis to Consider
History	
Early speech and gait impairment (lack of tremor, lack of motor asymmetry)	Atypical parkinsonism
Exposure to neuroleptics	Drug-induced parkinsonism
Onset prior to age 40	Genetic form of PD
Liver disease	Wilson disease, non-Wilsonian hepatolenticular degeneration
Early hallucinations and dementia with later development of PD features	Dementia with Lewy bodies
Diplopia, impaired down gaze	PSP
Poor or no response to an adequate trial of levodopa	Atypical or secondary parkinsonism
Physical Examination	
Dementia as first or early feature	Dementia with Lewy bodies
Prominent orthostatic hypotension	MSA-P
Prominent cerebellar signs	MSA-C
Slow saccades with impaired down gaze	PSP
High-frequency (6- to 10-Hz) symmetric postural tremor with a prominent kinetic component	Essential tremor

Abbreviations: MSA-C, multiple system atrophy–cerebellar type; MSA-P, multiple system atrophy–Parkinson type; PD, Parkinson disease; PSP, progressive supranuclear palsy.

monoxide, and particularly medications. The medications most likely to cause secondary parkinsonism are neuroleptic agents, including metoclopramide and chlorpromazine. Treatment of PD is typically with either levodopa-carbidopa or a dopamine agonist. Levodopa has a long history of use in PD dating to the 1960s. Levodopa is administered in combination with carbidopa to prevent peripheral conversion to dopamine and thus prevents side effects, especially nausea and vomiting. In Europe, levodopa is combined with benserazide to prevent this conversion. Levodopa is the most effective symptomatic treatment of PD. It improves motor features, quality of life, and life span as well as improving productive years of life with increased independence and employability. However, the majority of patients treated with levodopa develop motor complications with "on/off" periods, referring to fluctuations in motor responsiveness to the drug. In addition, patients may develop involuntary movements as well. Further, the duration of benefit of levodopa subsides over time to where it approaches the short half-life of the drug. Nondopaminergic features including falling, freezing, and autonomic dysfunction are also not treated with levodopa. Many providers now prefer dopamine agonists as first-line therapy. These drugs include pramipexole, ropinirole, and rotigotine as non-ergot derivatives. While these agents do not show comparable efficacy compared with levodopa, they are associated with fewer motor complications. It should be noted that even with use of the dopamine agonists, eventual treatment with levodopa is required in most patients. Selegiline is a monoamine oxidase inhibitor. While these agents can be used as monotherapy in early disease, there is a risk of serotonin syndrome when used with selective serotonin reuptake inhibitor agents such as fluoxetine. The risk is overall low, but as this patient is untreated, there are other better options for his care.

X-39. **The answer is C.** *(Chap. 427)* Deep brain stimulation (DBS) is the most common surgical therapy performed for Parkinson disease (PD). In this surgery, an electrode is placed into a target area, typically the subthalamic nucleus or globus pallidus pars interna. The electrode is connected to a stimulator usually placed in the chest wall. The precise mechanism by which DBS works is not known, but it is thought to act by disrupting the abnormal signal associated with PD and motor symptoms. Once placed, the DBS can be adjusted on many variables, including voltage, frequency, and pulse duration. The primary indication for DBS is severe tremor or levodopa-induced motor complications that cannot be controlled with medications. It does not improve features that fail to respond to levodopa including falling, freezing, and dementia.

X-40. **The answer is A.** *(Chap. 427)* This patient has Parkinson disease (PD). Clinically, PD is characterized by rest tremor, rigidity (stiffness), bradykinesia (slowing), and gait dysfunction with postural instability. These are known as the "cardinal features" of the disease. Additional clinical features can include freezing of gait, speech difficulty, swallowing impairment, autonomic disturbances, and a series of nonmotor features that include sensory alterations, mood disorders, sleep dysfunction, cognitive impairment, and dementia. Pathologically, the hallmark features of PD are degeneration of dopaminergic neurons in the substantia nigra pars compacta.

X-41. **The answer is D.** *(Chap. 428)* Parkinson disease is characterized by a resting tremor, essential tremor by a tremor that typically occurs while trying to sustain a posture coupled with an action tremor, and cerebellar dysfunction by a kinetic tremor and is usually associated with hypotonia and past pointing. Normal individuals can have a physiologic tremor that typically manifests as a mild, high-frequency (10–12 Hz), postural or action tremor typically affecting the upper extremities. This tremor is usually of no clinical consequence and often is only appreciated with an accelerometer or under stress. An enhanced physiologic tremor can be seen in up to 10% of the population, and it tends to occur in association with anxiety, fatigue, a metabolic disturbance (e.g., hyperthyroidism, electrolyte abnormalities), drugs (e.g., valproate, lithium), or toxins (e.g., caffeine, smoking, alcohol).

X-42. **The answer is C.** *(Chap. 428)* This is a case of essential tremor. Many cases are mild and require no treatment other than reassurance. Occasionally, tremor can be severe and interfere with eating, writing, and activities of daily living. This is more likely to occur as the patient ages and is often associated with a reduction in tremor frequency. Beta blockers and primidone are the standard drug therapies for essential tremor and help in about 50% of cases. Propranolol (20–120 mg daily, given in divided doses) is usually effective at relatively low doses, but higher doses may be needed in some patients. The drug is contraindicated in patients with bradycardia or asthma. Given this patient's healthy bradycardia, it would not be a good first choice. Primidone can be helpful but should be started at low doses (12.5 mg) and gradually increased (125–250 mg tid) to avoid sedation, nausea, and dizziness. Benefits have also been reported with gabapentin and topiramate, but these drugs have not been widely employed. Botulinum toxin injections may be helpful for limb or voice tremor, but treatment can be associated with muscle weakness.

X-43. **The answer is C.** *(Chap. 428)* Huntington disease (HD) is caused by an increase in the number of polyglutamine (CAG) repeats (>40) in the coding sequence of the *huntingtin* gene located on the short arm of chromosome 4. The larger the number of repeats, the earlier the disease is manifest and the faster the rate of clinical decline. Intermediate forms of the disease with 36–39 repeats are described in some patients, typically with less severe clinical involvement. Acceleration of the process tends to occur, particularly in males, with subsequent generations having larger numbers of repeats and earlier age of disease onset, a phenomenon referred to as anticipation. The gene encodes the highly conserved cytoplasmic protein huntingtin, which is widely distributed in neurons throughout the central nervous system, but whose function is largely unknown. Mitochondrial dysfunction has been demonstrated in the striatum and skeletal muscle of symptomatic and presymptomatic individuals. Fragments of the mutant huntingtin protein can be toxic, possibly by translocating into the nucleus and interfering with transcriptional regulation of proteins. Neuronal inclusions found in affected regions in HD may represent a protective mechanism aimed at segregating and facilitating the clearance of these toxic proteins. There is also interest in the possibility of protein accumulation and aggregation in HD, like Alzheimer's disease.

X-44. **The answer is F.** *(Chap. 429)* This patient is presenting with amyotrophic lateral sclerosis (ALS), a common motor neuron disease with an incidence of 1–3 per 100,000 population and prevalence of 3–5 per 100,000 population. ALS is responsible for about 1 in 1000 deaths in North America and Western Europe. This progressive disease has no curative treatment at this time, and it leads to disability and death due to respiratory failure within 3–5 years after diagnosis. The pathologic hallmark of ALS is loss or death of both upper and lower motor neurons. The upper motor neuron loss can be demonstrated by degeneration of the corticospinal tracts typically originating in layer five of the motor cortex and descending downward via the pyramidal tract to synapse with the lower motor neurons both directly and indirectly via interneurons. The lower motor neuron disease is manifested by death of anterior horn cells in the spinal cord and brainstem, which can lead to bulbar symptoms. Clinically, this leads to the classic findings of both upper and lower motor neuron disease in ALS. The most common presenting symptom in ALS is asymmetric weakness of insidious onset that is most prominent in the lower extremities. Muscle wasting and atrophy may be prominent. A detailed history can elicit cramping with volitional movements, such as stretching, which is most common in the early morning hours. Fasciculations may be identified. When the muscles of the hands are involved, extensor weakness is more common than flexor weakness. Bulbar symptoms include difficulty with chewing, swallowing, and movements of the face and tongue. Upper motor neuron symptoms may lead to spasticity with increased deep tendon reflexes. However, even in late stages of the disease, sensory and cognitive functions are preserved.

X-45. **The answer is E.** *(Chap. 429)* The spinal muscle atrophy disorders (SMAs) are a family of selective lower motor neuron diseases of early onset. Despite some phenotypic variability (largely in age of onset), the defect in the majority of families with SMA is loss of a protein (survival motor neuron) that is important in the formation and trafficking of RNA complexes across the nuclear membrane. Neuropathologically these disorders are characterized by extensive loss of large motor neurons; muscle biopsy reveals evidence of denervation atrophy. Several clinical forms exist. This patient likely has juvenile SMA

(SMA III, Kugelberg-Welander disease), which manifests during late childhood and runs a slow, indolent course. Unlike most denervating diseases, in this chronic disorder weakness is greatest in the proximal muscles; indeed, the pattern of clinical weakness can suggest a primary myopathy such as limb-girdle dystrophy. Electrophysiologic and muscle biopsy evidence of denervation distinguish SMA III from the myopathic syndromes.

X-46. **The answer is C.** *(Chap. 430)* Creutzfeldt-Jakob disease (CJD) is considered a prion disease. Prions are proteins that adopt an alternative conformation, which becomes self-propagating. Some prions cause degeneration of the central nervous system with the most prominent disease being CJD, which is caused by the prion protein PrP. CJD typically presents with a rapidly progressive dementia as well as motor abnormalities. The illness is relentlessly progressive and generally causes death within 9 months of onset. Most CJD patients are between 50 and 75 years of age; however, patients as young as 17 and as old as 83 have been recorded. There is no effective treatment for CJD. Four new concepts have emerged from studies of PrP prions. (1) Prions are the only known transmissible pathogens that are devoid of nucleic acid; all other infectious agents possess genomes composed of either RNA or DNA that direct the synthesis of their progeny. (2) Prion diseases may manifest as infectious, genetic, or sporadic disorders; no other group of illnesses with a single etiology presents with such a wide spectrum of clinical manifestations. (3) Prion diseases result from the accumulation of PrPSc, the conformation of which differs substantially from that of its precursor, PrPC. (4) Distinct strains of prions exhibit different biologic properties, which are epigenetically inherited. In other words, PrPSc can exist in a variety of different conformations, many of which seem to specify particular disease phenotypes.

X-47. **The answer is A.** *(Chap. 431)* In the patient who presents with ataxia, the rate and pattern of the development of cerebellar symptoms help to narrow the diagnostic possibilities. This patient has an acute ataxia, most suggestive of an intoxication (Table X-47). Acute and reversible ataxias include those caused by intoxication with alcohol, phenytoin, lithium, barbiturates, and other drugs. Intoxication caused by toluene exposure, gasoline sniffing, glue sniffing, spray painting, or exposure to methyl mercury or bismuth are additional causes of acute or subacute ataxia, as is treatment with cytotoxic chemotherapeutic drugs such as fluorouracil and paclitaxel. The Dix-Hallpike test or maneuver is a postural maneuver to elicit benign paroxysmal positional vertigo.

TABLE X-47 **Etiology of Cerebellar Ataxia**

Symmetric and Progressive Signs			Focal and Ipsilateral Cerebellar Signs		
Acute (Hours to Days)	Subacute (Days to Weeks)	Chronic (Months to Years)	Acute (Hours to Days)	Subacute (Days to Weeks)	Chronic (Months to Years)
Intoxication: alcohol, lithium, phenytoin, barbiturates (positive history and toxicology screen) Acute viral cerebellitis (CSF supportive of acute viral infection) Postinfection syndrome	Intoxication: mercury, solvents, gasoline, glue Cytotoxic chemotherapeutic drugs Alcoholic-nutritional (vitamin B_1 and B_{12} deficiency) Lyme disease	Paraneoplastic syndrome Antigliadin antibody syndrome Hypothyroidism Inherited diseases Tabes dorsalis (tertiary syphilis) Phenytoin toxicity Amiodarone	Vascular: cerebellar infarction, hemorrhage, or subdural hematoma Infectious: cerebellar abscess (mass lesion on MRI/CT, history in support of lesion)	Neoplastic: cerebellar glioma or metastatic tumor (positive for neoplasm on MRI/CT) Demyelinating: multiple sclerosis (history, CSF, and MRI are consistent) AIDS-related multifocal leukoencephalopathy (positive HIV test and CD4+ cell count for AIDS)	Stable gliosis secondary to vascular lesion or demyelinating plaque (stable lesion on MRI/CT older than several months) Congenital lesion: Chiari or Dandy-Walker malformations (malformation noted on MRI/CT)

Abbreviations: CSF, cerebrospinal fluid.

X-48. **The answer is B.** *(Chap. 432)* The patient is presenting with parkinsonism along with symptoms of orthostatic hypotension and constipation indicating concomitant autonomic dysfunction. As the patient exhibits no dementia and has no tremor, the most likely diagnosis would be multiple system atrophy (MSA). This rare disorder has a prevalence of about 2–5 per 100,000 and is commonly grouped within a category of disorders of atypical parkinsonism that includes progressive supranuclear palsy, corticobasal ganglionic degeneration, and frontotemporal dementia. MSA is typically diagnosed in the sixth decade of life and is slightly more common in men. MSA is characterized by degeneration of the substantia nigra pars compacta, striatum, cerebellum, and inferior olivary nuclei. Glial cytoplasmic inclusions that stain positive for α-synuclein is also a defining feature. The diagnosis of MSA should be suspected in individuals presenting with parkinsonian symptoms in combination with prominent cerebellar and/or autonomic complaints. In most patients, either cerebellar or parkinsonian symptoms predominate, leading to a subclassification of MSA-C or MSA-P. Autonomic symptoms occur in all patients. The most frequent autonomic symptoms include prominent orthostatic hypotension, severe constipation, neurogenic bladder, impotence in men, rapid eye movement–behavior disorder, and laryngeal stridor. Diagnosis is made by clinical features. Treatment with dopaminergic agents is typically ineffective. Management is primarily symptomatic and focused on managing the concomitant autonomic features. Orthostatic hypotension often requires fludrocortisone. If that approach fails, other agents including midodrine, ephedrine, pseudoephedrine, or phenylephrine may be used. Conservative treatment of the gastrointestinal and urinary symptoms include frequent small meals, stool softeners, bulking agents, and intermittent bladder catheterization. The median time to death after diagnosis is 10 years. Risk factors for decreased survival include female gender, urinary dysfunction, older age at onset, and parkinsonian variant of the disease.

X-49. **The answer is A.** *(Chap. 433)* This patient presents with trigeminal neuralgia, a relatively common disorder with an annual incidence of 4–8 cases per 100,000 population. It is more common in women and typically presents in middle-aged or elderly individuals. It presents as sharp, and sometimes excruciating, paroxysms of pain in the lips, gums, cheek, or chin. The pain typically lasts from just a few seconds to no more than a few minutes. The painful sensations recur frequently in clusters and can occur day or night. Episodes of pain can last for several weeks at a time. Pain can occur spontaneously, but is often elicited by light touch or movements of the affected areas, including chewing, speaking, or smiling. On physical examination, there are no objective signs of sensory or motor loss. Trigeminal neuralgia is caused by ectopic generation of action potentials by pain-sensitive afferent fibers in the fifth cranial nerve. Compression of the trigeminal nerve root by a blood vessel is believed to be the most common cause of trigeminal neuralgia. Demyelination near the entry of the fifth nerve root has also been implicated. Diagnosis of trigeminal neuralgia is made based on clinical features, and laboratory or radiologic examination is not required. There is no role for electromyography/nerve conduction studies in the evaluation of the disease. The initial treatment is typically with carbamazepine, which has been demonstrated to be effective in 50–75% of cases. The initial dose is 100 mg in two to three divided doses daily. The medication is titrated upward to achieve pain relief. Most patients require a dose of 200 mg qid or greater although doses >1200 mg daily confer no added benefit. For patients who do not tolerate carbamazepine, other antiseizure medications have been used to control the symptoms. These include oxcarbazepine, lamotrigine, and Dilantin. In cases that are refractory to medical therapy, microvascular surgical decompression can be considered and has a >70% success rate in relieving pain. Gamma knife radiosurgery may also be used. Radiofrequency thermal rhizotomy is used less frequently. Despite an initial success rate of >95% of individuals, up to one-third will have recurrence of symptoms, and the procedure is associated with an increased risk of complications including facial numbness and jaw weakness. The differential diagnosis of trigeminal neuralgia includes temporal arteritis, migraine or cluster headaches, and multiple sclerosis (MS). Temporal arteritis may present with superficial facial pain. One typically also has symptoms including jaw claudication, diffuse myalgias, and potential visual symptoms. Testing of erythrocyte sedimentation rate and performance of temporal artery biopsy are appropriate if this diagnosis is suspected. Migraine and cluster headaches present with a deeper sensation of pain. While the pain is often throbbing in nature, it lacks the stabbing quality of trigeminal neuralgia. MS can present with trigeminal neuralgia, but most patients have other symptoms of the disease as well, including weakness or visual symptoms. MS may be more likely if a patient presents with bilateral trigeminal neuralgia or at a young age, and an MRI would be appropriate at that time.

X-50. **The answer is B.** *(Chap. 443)* In acute Bell's palsy, there is inflammation of the facial nerve with mononuclear cells, consistent with an infectious or immune cause. Herpes simplex virus (HSV) type 1 DNA was frequently detected in endoneurial fluid and posterior auricular muscle, suggesting that a reactivation of this virus in the geniculate ganglion may be responsible for most cases. Reactivation of varicella-zoster virus is associated with Bell's palsy in up to one-third of cases and may represent the second most frequent cause. A variety of other viruses have also been implicated less commonly. There are many other causes of acute facial palsy that must be considered in the differential diagnosis of Bell's palsy. Lyme disease can cause unilateral or bilateral facial palsies; in endemic areas, ≥10% of cases of facial palsy are likely due to infection with *Borrelia burgdorferi*. Facial palsy that is often bilateral occurs in sarcoidosis and in Guillain-Barré syndrome. Leprosy frequently involves the facial nerve, and facial neuropathy may also occur in diabetes mellitus, connective tissue diseases including Sjögren syndrome, and amyloidosis. The rare Melkersson-Rosenthal syndrome consists of recurrent facial paralysis; recurrent, and eventually permanent, facial (particularly labial) edema; and, less constantly, plication of the tongue. Its cause is unknown. Acoustic neuromas frequently involve the facial nerve by local compression. Infarcts, demyelinating lesions of MS, and tumors are the common pontine lesions that interrupt the facial nerve fibers; other signs of brainstem involvement are usually present. Tumors that invade the temporal bone (carotid body, cholesteatoma, dermoid) may produce a facial palsy, but the onset is insidious and the course progressive.

X-51. **The answer is D.** *(Chap. 433)* Symptomatic measures for Bell's palsy include (1) the use of paper tape to depress the upper eyelid during sleep and prevent corneal drying, (2) artificial tears, and (3) massage of the weakened muscles. A course of glucocorticoids, given as prednisone 60–80 mg daily during the first 5 days and then tapered over the next 5 days, modestly shortens the recovery period and improves the functional outcome. Although large and well-controlled randomized trials found no added benefit of the antiviral agents valacyclovir (1000 mg daily for 5–7 days) or acyclovir (400 mg five times daily for 10 days) compared with glucocorticoids alone, some earlier data suggested that combination therapy with prednisone plus valacyclovir might be marginally better than prednisone alone, especially in patients with severe clinical presentations. For patients with permanent paralysis from Bell's palsy, a number of cosmetic surgical procedures have been used to restore a relatively symmetric appearance to the face.

X-52. **The answer is F.** *(Chap. 434)* This patient presents with spinal cord compression, which represents an urgent need for treatment. Spinal cord compression can occur with any tumor, but is most common with tumors of the breast, lung, prostate, kidney, lymphoma, and myeloma. The thoracic spinal column is the most commonly affected area for most tumors. However, metastases from prostate or ovarian cancer may invade locally into the spinal canal. Thus, they more commonly affect the sacral and lumbar vertebrae. Pain is typically the initial symptom of vertebral metastases. The pain can be dull and aching or sharp with radiating pain. The pain is usually worsened by movement, cough, sneezing, and at night. When spinal cord compression occurs, the patient will develop weakness, sensory abnormalities, and bowel or bladder dysfunction. When spinal cord compression is suspected, imaging should be obtained promptly. Diagnosis typically is made with MRI, which also allows one to differentiate between metastasis, epidural abscess, epidural hemorrhage, or other lesions. On T1-weighted MRI, the vertebral metastases will appear hypodense relative to normal bone marrow. With gadolinium administration, the MRI may pseudo-normalize as uptake of the contrast causes the lesions to appear at the same density as the bone marrow. Plain radiographs of the spine and radionuclide bone scans will not identify 10–20% of metastatic lesions. Management of cord compression should include glucocorticoids, local radiotherapy, and treatment of the underlying malignancy. Glucocorticoids decrease cord edema, and dexamethasone is the most commonly utilized medication. Up to 40 mg daily of dexamethasone is frequently used. Prompt treatment with radiotherapy to the area of cord compression is essential to decrease morbidity associated with the finding. A good response to therapy is expected for individuals who are ambulatory at the time of presentation. If motor deficits persist for longer than 12 hours, these, however, will not improve. Treatment would be expected to prevent new weakness. Finally, specific therapy for the underlying tumor type is important. Surgical decompression of cord compression is generally not a preferred therapy. If there is only a single metastasis to the spine, it can sometimes be considered as a therapy. Otherwise, surgical therapy is typically limited to those individuals who fail to respond to the maximum-tolerated dose of radiotherapy.

X-53. **The answer is C.** *(Chap. 434)* This patient likely has sarcoidosis, an important cause of acute or subacute myelopathy. It most often presents with slowly progressive weakness or a relapsing-remitting course. The patient affected with sarcoid myelopathy typically has concomitant sensory loss with weakness. A distinct cord level may be demonstrated. The MRI often shows diffuse edema of the spinal cord with gadolinium enhancement in active lesions. Nodular enhancement of the adjacent surface of the spinal cord is frequently seen, and the disease may affect many levels of the spinal cord. A lumbar puncture shows a lymphocytic predominant cell count with mildly elevated cerebrospinal fluid protein. As sarcoidosis is often a multisystem disease, examination for evidence of disease outside of the spinal cord should be performed, including chest imaging, slit lamp eye examination, serum calcium levels, and electrocardiogram. If there is evidence of abnormalities in other body systems, then definitive diagnosis can be made with a biopsy demonstrating non-caseating granulomas on pathologic examination. Patients are treated initially with high-dose glucocorticoids to decrease swelling and stimulate regression of the granulomatous lesions. Many patients will also require alternative immunosuppression including azathioprine, mycophenolate mofetil, or infliximab. The presence of caseating granulomas typically signifies an infectious process, most commonly tuberculosis or fungal infection. Atypical lymphocytes with clonality on flow cytometry are found in various types of lymphoma. A biopsy with small round cells that often resemble lymphocytes that demonstrate scant cytoplasm, indistinct nucleoli, and mitotic figures is typical of small cell lung carcinoma. Nonspecific chronic inflammation is nondiagnostic and further workup would be required.

X-54. **The answer is D.** *(Chap. 434)* Syringomyelia is a developmental disorder of the spinal cord that results in enlargement of the central cavity of the spinal cord. More than half of all cases are associated with a concomitant Chiari I malformation of the brainstem with protrusion of the cerebellar tonsils through the foramen magnum and into the cervical spinal canal. Although controversial, one theory for the pathogenesis of syringomyelia is impaired cerebrospinal fluid flow with secondary enlargement of the central spinal cord, and the common coexistence with Chiari malformations may provide support for this theory. Symptoms of syringomyelia develop gradually, often beginning in late adolescence or early adulthood. The symptoms progress irregularly and may even arrest for a prolonged period. The presentation of syringomyelia typically includes both sensory loss and muscle wasting and weakness. The sensory disturbance is dissociative with loss of pain and temperature sensation, but preservation of vibration and touch. Patients may present with injuries or burns that occur when the patient is unaware of a painful sensation in the affected limb. The distribution of sensory loss is classically described as cape-like, affecting the nape of the neck, shoulders, upper arms, and hands. Patients are areflexic in the upper limbs. Symptoms may be asymmetric. As the cavity enlarges, it can further lead to spasticity and weakness in the lower extremities as well. There are no definitive treatment options for the disease. If a Chiari malformation is also present, surgical decompression may be required. Surgeons have attempted direct decompression of the spinal canal with varied results.

X-55. **The answer is E.** *(Chap. 436)* Ocrelizumab is a humanized monoclonal antibody directed against the CD20 molecule present on the surface of mature B cells. In two phase 3 trials, ocrelizumab demonstrated a high degree of efficacy against relapsing multiple sclerosis (MS), reducing annualized relapse rates by 47%, reducing new MRI lesions by 95%, and improving other measures of inflammatory and degenerative disease activity, compared with three times per week interferon β-1a (Rebif) (Table X-55). Natalizumab is a humanized monoclonal antibody directed against the α4-subunit of α4β1 integrin, a cellular adhesion molecule expressed on the surface of lymphocytes. It is highly effective in reducing the attack rate and significantly improves all measures of disease severity

TABLE X-55 **Outcomes for FDA-Approved Therapies for Multiple Sclerosis (MS)[a]**

Relapsing MS						
			Clinical Outcomes[b]		MRI Outcomes[c]	
Dose, Route, and Schedule	Study Duration Weeks	Comparator	Attack Rate (Mean)	Change in Disease Severity	New T2 Lesions[d]	Total Burden of Disease
IFN-β-1b, 250 μg SC qod	96	PBO	–34%[e]	–29% (NS)	–83%[f]	–17%[e]
IFN-β-1a, 30 μg IM qw	96	PBO	–18%[g]	–37%[g]	–36%[f]	NS
IFN-β-1a, 44 μg SC tiw	96	PBO	–32%[e]	–30%[g]	–78%[e]	–15%[e]
Peg-IFN-β-1a, 125 μg SC q2w	48	PBO	–36%[e]	–38%[g]	–67%[e]	–2%[e]
GA, 20 mg SC qd	96	PBO	–29%[f]	–12% (NS)	–38%[f]	–8%[f]
MTX, 12 mg/m^2 IV q3mo	96	PBO	–66%[e]	–75%[g]	–79%[g]	NR
NTZ, 300 mg IV qmo	96	PBO	–68%[e]	–42%[e]	–83%[e]	–18%[e]
FNG, 0.5 mg PO qd	96	PBO	–55%[e]	–34%[f]	–74%[e]	–23%[e]
DMF, 240 mg PO bid	96	PBO	–52%[e]	–40%[f]	–71%[e]	NR
TF, 14 mg PO qd	96	PBO	–31%[e]	–26%[g]	–70%[e]	–20%[g]
FNG, 0.5 mg PO qd	48	IFN-β-1a, 30 μg IM qw	–52%[e]	NS	–35%[e]	NS
ALEM, 12 mg/m^2 IV/5 d	104	IFN-β-1a, 44 μg SC tiw	–49%[e]	–42%[f]	–32%[e]	NS
OCR, 600 mg IV, q6mo	96	IFN-β-1a, 44 μg SC tiw	–46%[e,h]	–33%[e,h]	–80%[e,h]	NR
Primary Progressive MS						
OCR, 600 mg IV, q6mo	96	PBO	–NR	–24%	–92%	–11%

[a] Percentage reductions (or increases) have been calculated by dividing the reported rates in the treated group by the comparable rates in the placebo group, except for MRI disease burden, which was calculated as the difference in the median percentage change between the treated and placebo group.

[b] Severity = 1 point Expanded Disability Status Score progression, sustained for 3 months (in the IFN-β-1a 30 μg qw trial, this change was sustained for 6 months; in the IFN-β-1b trial, this was over 3 years).

[c] Different studies measured these MRI measures differently, making comparisons difficult (numbers for new T2 represent the best-case scenario for each trial).

[d] New lesions seen on T2-weighted MRI.

[e] $p = 0.001$.

[f] $p = 0.01$.

[g] $p = 0.05$.

[h] Pooled analysis from OPERA 1 and 2 studies.

Abbreviations: ALEM, alemtuzumab; DMF, dimethyl fumarate; FDA, U.S. Food and Drug Administration; FNG, fingolimod; GA, glatiramer acetate; IFN-β, interferon β; MTX, mitoxantrone; NR, not reported; NS, not significant; NTZ, natalizumab; OCR, ocrelizumab; PBO, placebo; qmo, once per month; qod, every other day; qw, once per week; SC, subcutaneous; TF, teriflunomide; tiw, three times per week.

in MS (both clinical and MRI). Dimethyl fumarate (DMF) is a small molecule and is a Krebs cycle metabolite with anti-inflammatory effects in psoriasis. Although the precise mechanisms of action of DMF are not fully understood, it seems to modulate the expression of proinflammatory and anti-inflammatory cytokines. Also, DMF inhibits the ubiquitylation and degradation of nuclear factor E2-related factor 2, a transcription factor that binds antioxidant response elements located on DNA and induces transcription of several antioxidant proteins. Fingolimod is a sphingosine-1-phosphate inhibitor that prevents the egress of lymphocytes from secondary lymphoid organs such as the lymph nodes and spleen. Its mechanism of action is probably due to sequestration of lymphocytes in the periphery, thereby inhibiting their trafficking to the central nervous system (CNS). Interferon β is a class I interferon originally identified by its antiviral properties. Efficacy in MS probably results from immunomodulatory properties including (1) downregulating expression of major histocompatibility complex molecules on antigen-presenting cells, (2) reducing proinflammatory and increasing regulatory cytokine levels, (3) inhibiting T-cell proliferation, and (4) limiting the trafficking of inflammatory cells in the CNS.

X-56. and X-57. **The answers are C and D, respectively.** *(Chap. 436)* This patient presents with visual disturbance and weakness affecting the lower extremities with a past history of prior visual disturbance. This suggests a diagnosis of multiple sclerosis (MS), an autoimmune demyelinating disorder of the central nervous system. This disease affects about 350,000 individuals in the United States and has a variable clinical course, with some individuals experiencing limited symptoms and others becoming very incapacitated due to the disease. MS is three times more common in women, with a typical age of onset between 20 and 40 years of age. MS is more common in white individuals that those of African or Asian descent. In addition, geographic variations in disease prevalence have also been demonstrated, with higher prevalence in the temperate zone areas of northern North America, northern Europe, and southern Australia and New Zealand. In contrast, the tropics have a prevalence that is 10–20 times less. Other well-established risk factors for development of MS include vitamin D deficiency, exposure to Epstein-Barr virus after early childhood, and cigarette smoking. Despite the fact that this is an autoimmune disorder, there has been no association between MS and other autoimmune disorders. The clinical manifestations of MS are varied. The disease can present with an abrupt onset of symptoms or may develop gradually. The most common initial presenting symptoms include sensory loss, optic neuritis, weakness, paresthesias, and diplopia. Weakness of the limbs may be asymmetric and manifest as loss of strength, speed, dexterity, or endurance. Symptoms are upper neuron in origin and have associated spasticity, hyper-reflexia, and Babinski sign most commonly. However, if there is a spinal cord lesion, lower motor neuron signs and loss of reflexes may also be seen. The spasticity that is present may lead to spontaneous or movement-induced muscle spasms and affects up to 30% of patients with MS. Optic neuritis presents with blurred vision, dimness, or decreased color perception in the central visual fields. Visual symptoms typically only affect one eye. Periorbital pain often precedes or accompanies visual loss. Funduscopic examination may be normal or show optic disc swelling. Other common symptoms that occur with MS include bladder dysfunction, ataxia, constipation, chronic pain, fatigue, and depression. A diagnosis of MS can be difficult to confirm in some individuals. There is no definitive test for MS. The diagnostic criteria require two or more episodes of symptoms and two or more signs of dysfunction in noncontiguous white matter tracts. MRI characteristically shows multiple hyperintense T2-weighted lesions that can be present in the brain, brainstem, and spinal cord. More than 90% of lesions seen on MRI, however, are asymptomatic. Approximately one-third of lesions that appear hyperintense on T2-weighted images will be hypointense on T1-weighted images. These "black holes" may be a marker of irreversible demyelination and axonal loss. Evoked potentials are no longer commonly used in MS and are most useful in studying pathways that are not exhibiting clinical symptoms. Evoked potentials are not specific to MS, although a marked delay in latency of transmission suggests demyelination. The cerebrospinal fluid (CSF) may show an increased number of mononuclear cells, although CSF protein is typically normal. Oligoclonal bands help to assess the intrathecal production of IgG. The presence of two or more discrete oligoclonal bands in the CSF that are not present in serum is found in more than 75% of MS patients. If a patient has a pleocytosis of >75 cells/μL, presence of polymorphonuclear cells, or protein concentration >100 mg/dL, an alternative diagnosis should be sought.

X-58. **The answer is A.** *(Chap. 437)* Neuromyelitis optica (NMO) is an autoimmune disease associated with a highly specific autoantibody directed against aquaporin-4 (AQP4) that is present in the sera of ~70% of patients with a clinical diagnosis of NMO. AQP4 is localized to the foot processes of astrocytes in close apposition to endothelial surfaces, as well as at paranodal regions near nodes of Ranvier. It is likely that AQP4 antibodies are pathogenic because passive transfer of AQP4 antibodies into laboratory animals can reproduce histologic features of the disease; complement fixation is thought to mediate astrocyte injury. Because of the high specificity of the antibody, its presence is considered to be diagnostic when found in conjunction with a typical clinical presentation. Anti-AQP4 seropositive patients have a high risk for future relapses; more than half will relapse within 1 year if untreated. Anti-cyclic citrullinated peptide antibodies are found in rheumatoid arthritis. Anti–double-stranded DNA antibodies occur in systemic lupus erythematosus and are associated with the development of nephritis. Anti-myeloperoxidase antibodies are a subtype of anti-neutrophil cytoplasmic antibodies (ANCA) found in ANCA-associated vasculitis. The tRNA synthetases are targeted in some forms of myositis (e.g., anti-Jo1 antibodies in dermatomyositis or anti-synthetase syndrome).

X-59. **The answer is E.** *(Chap. 437)* Neuromyelitis optica (NMO; Devic disease) is an aggressive inflammatory disorder characterized by recurrent attacks of optic neuritis (ON) and myelitis. An important consideration, especially early in its presentation, is distinguishing between NMO and multiple sclerosis (MS). In patients with NMO, attacks of ON can be bilateral and produce severe visual loss (uncommon in MS); myelitis can be severe and transverse (which is rare in MS) and is typically longitudinally extensive involving three or more contiguous vertebral segments. Also in contrast to MS, progressive symptoms typically do not occur in NMO. The brain MRI was earlier thought to be normal in NMO, but it is now recognized that in many cases brain lesions are present including areas of nonspecific signal change as well as lesions associated with specific syndromes such as the hypothalamus causing an endocrinopathy; the area postrema in the lower medulla presenting as intractable hiccoughs or vomiting; or the cerebral hemispheres producing focal symptoms, encephalopathy, or seizures. Large MRI lesions in the cerebral hemispheres can be asymptomatic, sometimes have a "cloud-like" appearance and, unlike MS lesions, are often not destructive, and can resolve completely. Spinal cord MRI lesions typically consist of focal enhancing areas of swelling and tissue destruction, extending over three or more spinal cord segments, and on axial sequences, these are centered on the gray matter of the cord. Cerebrospinal fluid findings include pleocytosis greater than that observed in MS, with neutrophils and eosinophils present in many acute cases; oligoclonal bands are uncommon, occurring in <20% of NMO patients. Both MS and NMO are more common in women than in men.

X-60. **The answer is C.** *(Chap. 438)* Hydroxychloroquine can cause a toxic myopathy characterized by slowly progressive, painless, proximal weakness and atrophy, which is worse in the legs than the arms. In addition, neuropathy can also develop with or without the myopathy leading to sensory loss and distal weakness. The "neuromyopathy" usually appears in patients taking 500 mg daily for a year or more but has been reported with doses as low as 200 mg/d. Serum creatine kinase levels are usually elevated due to the superimposed myopathy. Nerve conduction studies (NCSs) reveal mild slowing of motor and sensory nerve conduction velocities with a mild to moderate reduction in the amplitudes, although NCSs may be normal in patients with only the myopathy. Electromyography demonstrates myopathic muscle action potentials (MUAPs), increased insertional activity in the form of positive sharp waves, fibrillation potentials, and occasionally myotonic potentials, particularly in the proximal muscles. Neurogenic MUAPs and reduced recruitment are found in more distal muscles. In this patient with clinical and NCS findings consistent with hydroxychloroquine myopathy and neuropathy. Between 2 and 27% of individuals with systemic lupus erythematosus develop peripheral neuropathy. Affected patients typically present with a slowly progressive sensory loss beginning in the feet. Some patients develop burning pain and paresthesia with normal reflexes, and NCSs suggest a pure small-fiber neuropathy. Less common are multiple mononeuropathies presumably secondary to necrotizing vasculitis. Rarely, a generalized sensorimotor polyneuropathy meeting clinical, laboratory, electrophysiologic, and histologic criteria for either Guillain-Barré syndrome (GBS) or chronic inflammatory demyelinating polyneuropathy (CIDP) may occur. A patient with GBS or CIDP would be expected to have an abnormal lumbar puncture. Similarly, the normal lumbar puncture and clinical presentation is not consistent with multiple sclerosis.

X-61. **The answer is E.** *(Chap. 438)* Vitamin B_6, or pyridoxine, can produce neuropathic manifestations from both deficiency and toxicity. The polyneuropathy of vitamin B_6 is nonspecific, manifesting as a generalized axonal sensorimotor polyneuropathy and not a radiculopathy. Radiculopathies are most often due to compression from degenerative joint disease and herniated disks, but there are a number of unusual etiologies (Table X-61). Degenerative spine disease affects a number of different structures, which narrow the diameter of the neural foramen or canal of the spinal column and compromise nerve root integrity.

X-62. **The answer is A.** *(Chap. 438)* Charcot-Marie-Tooth (CMT) syndrome is the most common type of hereditary neuropathy. CMT is comprised of several similar but genetically distinct conditions with different associated mutations. CMT1 is the most common syndrome and is an inherited demyelinating sensorimotor neuropathy. CMT1 most often affects patients in the first to third decades of life with distal leg weakness (i.e., foot drop).

TABLE X-61 Causes of Radiculopathy

- Herniated nucleus pulposus
- Degenerative joint disease
- Rheumatoid arthritis
- Trauma
- Vertebral body compression fracture
- Pott disease
- Compression by extradural mass (e.g., meningioma, metastatic tumor, hematoma, abscess)
- Primary nerve tumor (e.g., neurofibroma, schwannoma, neurinoma)
- Carcinomatous meningitis
- Perineurial spread of tumor (e.g., prostate cancer)
- Acute inflammatory demyelinating polyradiculopathy
- Chronic inflammatory demyelinating polyradiculopathy
- Sarcoidosis
- Amyloidoma
- Diabetic radiculopathy
- Infection (Lyme disease, herpes zoster, HIV, cytomegalovirus, syphilis, schistosomiasis, *Strongyloides*)
- Arachnoiditis (e.g., postsurgical)
- Radiation

There are several subtypes of *CMT1*, most of which are inherited in an autosomal dominant fashion. However, the penetrance is variable, and some affected family members may remain asymptomatic even late in life. The most common genetic defect in *CMT1* (*CMT1A*) is a 1.5-megabase duplication in the gene for peripheral myelin production (*PMP-22*) on chromosome 17. This results in a patient having three copies of the gene rather than two. Although patients generally do not complain of sensory symptoms, these can be elicited often on physical examination. Muscle stretch reflexes are unobtainable or reduced throughout, and muscles below the knee are often atrophied, which makes legs appear to have so-called inverted champagne bottle appearance. There are no medical therapies for *CMT*, but patients are generally referred for physical and occupational therapy. Bracing and other orthotic devices are frequently used. Hereditary neuralgic amyotrophy is an autosomal dominant disorder characterized by recurrent attacks of pain, weakness, and sensory loss in the distribution of the brachial plexus that often begins in childhood. Hereditary sensory and autonomic neuropathy is a rare group of hereditary neuropathies in which sensory and autonomic dysfunction predominates over muscle weakness. This would not fit the clinical pattern described here. Guillain-Barré syndrome generally presents acutely with rapid development of ascending paralysis. The prolonged symptom period and distribution described here are not typical for Guillain-Barré syndrome. Fabry disease is an X-linked disorder in which men are more commonly affected then women.

Patients have angiokeratomas, which are reddish-purple lesions usually found around the umbilicus, scrotum, and inguinal region. Burning pain in the hands and feet often is found in late childhood or early adult life. Patients also have premature atherosclerosis from the underlying mutation in the α-galactosidase gene with accumulation of ceramide in nerves and blood vessels.

X-63. The answer is C. *(Chap. 438)* Diabetes mellitus is the most common cause of peripheral neuropathy in developed countries and is associated with several different types of polyneuropathy including distal symmetric sensory or sensorimotor polyneuropathy, autonomic neuropathy, diabetic neuropathic cachexia, polyradicular neuropathies, cranial neuropathies, and other mononeuropathies. Risk factors for development of neuropathy include long-standing and poorly controlled diabetes and the presence of retinopathy or nephropathy. The patient here appears to have diabetic distal symmetric sensory and sensorimotor polyneuropathy (DSPN), which is the most common form of diabetic neuropathy. DSPN presents with sensory loss beginning in the toes and gradually progresses over time up the legs and into the fingers and arms. Symptoms also may include tingling, burning, and deep aching pains. Nerve biopsy, although rarely indicated, often shows axonal degeneration, endothelial hyperplasia, and occasionally perivascular inflammation.

Tight glucose control prevents development of disease but does not reverse established disease. Diabetic autonomic neuropathy is often seen in combination with DSPN and manifests by abnormal sweating, dysfunctional thermoregulation, dry eyes and mouth, postural hypotension, gastrointestinal abnormalities including gastroparesis, and genitourinary dysfunction.

X-64. **The answer is D.** *(Chap. 439)* In the vast majority of patients with Guillain-Barré (GBS), treatment should be initiated as soon after diagnosis as possible. Each day counts; ~2 weeks after the first motor symptoms, it is not known whether immunotherapy is still effective. If the patient has already reached the plateau stage, then treatment probably is no longer indicated, unless the patient has severe motor weakness and one cannot exclude the possibility that an immunologic attack is still ongoing. Either high-dose IVIg or plasmapheresis can be initiated, as they are equally effective for typical GBS. A combination of the two therapies is not significantly better than either alone. IVIg is often the initial therapy chosen because of its ease of administration and good safety record. Anecdotal data have also suggested that IVIg may be preferable to plasma exchange (PE) for the acute motor axonal neuropathy and Miller Fisher syndrome variants of GBS. IVIg is administered as five daily infusions for a total dose of 2 g/kg body weight. There is some evidence that GBS autoantibodies are neutralized by anti-idiotypic antibodies present in IVIg preparations, perhaps accounting for the therapeutic effect. A course of plasmapheresis usually consists of ~40–50 mL/kg PE four to five times over 7–10 days. Meta-analysis of randomized clinical trials indicates that treatment reduces the need for mechanical ventilation by nearly half (from 27 to 14% with PE) and increases the likelihood of full recovery at 1 year (from 55 to 68%). Functionally significant improvement may occur toward the end of the first week of treatment or may be delayed for several weeks. The lack of noticeable improvement following a course of IVIg or PE is not an indication to treat with the alternate treatment. However, there are occasional patients who are treated early in the course of GBS and improve, who then relapse within a month. Brief retreatment with the original therapy is usually effective in such cases. Glucocorticoids have not been found to be effective in GBS. Occasional patients with very mild forms of GBS, especially those who appear to have already reached a plateau when initially seen, may be managed conservatively without IVIg or PE.

X-65. **The answer is B.** *(Chap. 439)* Guillain-Barré syndrome (GBS) is an acute demyelinating polyneuropathy that can be severe and life-threatening if not immediately recognized and treated. Each year, there are about 5000–6000 cases in the United States, with an incidence of about 1–4 cases per 100,000 population annually. Men are slightly more commonly affected than women, and GBS is more commonly diagnosed in adulthood. The typical presentation is a rapid ascending paralysis that may be first noticed as weak or "rubbery" legs. The weakness can evolve over hours to a few days, with the legs being more affected than the arms. Tingling dysesthesias are also frequently present, although sensory neuropathy is always present. Facial paresis occurs in about 50% of patients, and other lower cranial nerves may also be affected. Pain is a frequent complaint, with pain in the neck, shoulders, back, and diffusely over the spine. In addition, vague sensation of deep aching pain in the weakened muscles may also be present. Up to 30% of patients will require mechanical ventilation due to weakness of the respiratory muscles. Moreover, bulbar involvement increases the risk of aspiration and subsequent pneumonia. Deep tendon reflexes are decreased or disappear entirely within the first few days of onset. Cutaneous sensory deficits are usually only mild if present at all. Bladder dysfunction only rarely occurs and is transient. Persistent or severe bladder dysfunction should stimulate a workup for other causes. Autonomic symptoms are common. Blood pressure may be quite labile with marked postural changes. Cardiac dysrhythmias may also occur and require continuous monitoring. Typically within 4 weeks of onset or sooner, there is a plateau in symptoms with no further progression. Diagnosis of GBS relies on a high degree of clinical suspicion because there is no one test that is diagnostic for the disorder. Typical cerebrospinal fluid (CSF) findings include a high CSF protein without pleocytosis. The presence of a high CSF white blood cell count should prompt a search for an alternative diagnosis. Early in the disease process, electrodiagnostic testing may be normal or only show mild findings of demyelination. Approximately 70% of GBS cases occur within 1–3 weeks of an antecedent infectious illness. Most commonly, the illness is respiratory or gastrointestinal in nature. About 20–30% of all cases in North America, Europe, and Australia are preceded by infection or reinfection with *Campylobacter jejuni*. A similar proportion of individuals will have had an infection with a human herpes virus, most often cytomegalovirus or Epstein-Barr virus. Less frequently, HIV, hepatitis E, or *Mycoplasma pneumoniae* may be implicated. Recent immunizations are a rare cause of GBS, with a risk of <1 per million.

X-66. **The answer is A.** *(Chap. 440)* Myasthenia gravis (MG) is a relatively common neuromuscular disorder that is caused by antibody-mediated autoimmune destruction of acetylcholine receptors at the neuromuscular junction. MG has a prevalence of about 2–7 in 10,000 individuals and affects women more commonly than men at a ratio of 3:2. The age of presentation in women is generally in the 20s to 30s, whereas men more commonly present in their 50s and 60s. The key features of MG are weakness and fatigability of muscles. The weakness increases with repeated use and is typically more prominent late in the day. The distribution of muscle weakness often follows a typical pattern, with cranial muscles being affected early in the course of disease. Common clinical features include diplopia, ptosis, inability to smile fully, weakness with chewing, dysarthria, and dysphagia. Aspiration of liquids may also occur. In the majority of patients, the weakness becomes generalized, affecting proximal muscles greater than distal muscles. Deep tendon reflexes are preserved, and the disease may be asymmetric. The diagnosis is suspected after the appearance of the characteristic symptoms and signs. The diagnosis should be confirmed with further testing because treatment may involve surgery and the prolonged use of immunosuppressive agents. The most sensitive test for the diagnosis of MG is the presence of antibodies to the acetylcholine receptor (AChR). These antibodies are present in about 85% of patients with MG. The presence of AChR antibodies in a patient with typical signs and symptoms is diagnostic. If AChR antibodies are negative, additional testing for muscle-specific kinase antibodies will be positive in another 40% of individuals. However, if the disease is limited to the ocular muscles alone, both of these tests are likely to be negative. Use of repetitive nerve stimulation characteristically shows decrements of >10–15% in action potential amplitude with successive electric shocks delivered at two to three per second. Patients should be tested with repetitive stimulation in a proximal muscle group or in muscles that have been demonstrated to be weakened in the disease. Edrophonium is an acetylcholinesterase inhibitor that allows acetylcholine to interact repeatedly with the limited number of AChRs, producing improvement in the strength of myasthenic muscles. An objective end point must be chosen when performing the edrophonium test to determine whether there is an improvement in muscle strength after administration. At this time, edrophonium is only used in individuals with suspected MG with negative antibody testing as well as negative electrodiagnostic testing. False-positive tests may occur in patients with other neurologic diseases, such as amyotrophic lateral sclerosis. Antibodies to voltage-gated calcium channels are found in patients with Lambert-Eaton syndrome, another neuromuscular disorder associated with complaints of weakness. In this disorder, however, individuals develop improved responses with repetitive nerve stimulation. Clinically, Lambert-Eaton syndrome can also be distinguished from MG because Lambert-Eaton syndrome typically has prominent autonomic changes as well as depressed deep tendon reflexes.

X-67. **The answer is E.** *(Chap. 440)* Myasthenic patients have an increased incidence of several associated disorders (Table X-67). Thymic abnormalities occur in ~75% of acetylcholine receptor antibody–positive patients. Neoplastic change (thymoma) may produce enlargement of the thymus, which is detected by chest CT. A thymic shadow on CT scan may normally be present through young adulthood, but enlargement of the thymus in a patient age >40 years is highly suspicious of thymoma. Hyperthyroidism occurs in 3–8% of patients and may aggravate the myasthenic weakness. Thyroid function tests should be obtained in all patients with suspected myasthenia gravis (MG). Other autoimmune disorders, most commonly systemic lupus erythematosus and rheumatoid arthritis, can coexist with MG; associations also occur with neuromyelitis optica, neuromyotonia, Morvan syndrome (encephalitis, insomnia, confusion, hallucinations, autonomic dysfunction, and neuromyotonia), rippling muscle disease, granulomatous myositis/myocarditis, and chronic inflammatory demyelinating polyneuropathy. Chronic kidney disease and

TABLE X-67 Disorders Associated with Myasthenia Gravis and Recommended Laboratory Tests

Associated Disorders
Disorders of the thymus: thymoma, hyperplasia
Other autoimmune neurological disorders: chronic inflammatory demyelinating polyneuropathy, neuromyelitis optica
Other autoimmune disorders: Hashimoto thyroiditis, Graves disease, rheumatoid arthritis, systemic lupus erythematosus, skin disorders, family history of autoimmune disorder
Disorders or circumstances that may exacerbate myasthenia gravis: hyperthyroidism or hypothyroidism, occult infection, medical treatment for other conditions (see Table 440-4 in HPIM 20)
Disorders that may interfere with therapy: tuberculosis, diabetes, peptic ulcer, gastrointestinal bleeding, renal disease, hypertension, asthma, osteoporosis, obesity
Recommended Laboratory Tests or Procedures
CT or MRI of chest
Tests for antinuclear antibodies, rheumatoid factor
Thyroid function tests
Testing for tuberculosis
Fasting blood glucose, hemoglobin A1c
Pulmonary function tests
Bone densitometry

diabetes mellitus are not associated with MG but can complicate its treatment. An infection of any kind can exacerbate typical MG, and should be sought carefully in patients with relapses. Because of the side effects of glucocorticoids and other immunotherapies used in the treatment of MG, a thorough medical investigation should be undertaken, searching specifically for evidence of chronic or latent infection (such as tuberculosis or hepatitis), hypertension, diabetes, renal disease, and glaucoma.

X-68. **The answer is E.** *(Chap. 440)* In patients with generalized myasthenia gravis (MG) who have symptoms despite pyridostigmine, the next consideration is thymectomy (Figure X-68). Until recently there was a debate regarding the role of thymectomy in non-thymomatous MG, but a recent large international trial of extended transsternal thymectomy in non-thymomatous acetylcholine receptor antibody–positive, generalized MG demonstrated that participants who underwent thymectomy had improved strength and function, required less prednisone and additions of second-line agents (e.g., azathioprine), and fewer hospitalizations for exacerbations and therefore is currently recommended for some patients. Whether or not less invasive thymectomy may be beneficial is unknown. Also, patients with ocular myasthenia, muscle-specific kinase–positive, and seronegative MG were excluded from the study; retrospective and anecdotal evidence suggest that these patients may not benefit from thymectomy. Thymectomy should never be carried out as an emergency procedure, but only when the patient is adequately prepared. If necessary, treatment with IVIg or plasmapheresis may be used before surgery to maximize strength in weak patients. Mycophenolate, azathioprine, plasmapheresis, and IVIg all have efficacy in myasthenia gravis and may be used in the future for this patient.

X-69. **The answer is E.** *(Chap. 441)* Endocrinopathies can cause weakness, but fatigue is more common than true weakness. The serum creatine kinase (CK) level is often normal (except in hypothyroidism) and the muscle histology is characterized by atrophy rather than destruction of muscle fibers. Nearly all endocrine myopathies respond to appropriate treatment. Patients with hypothyroidism have frequent muscle complaints, and about one-third have proximal muscle weakness. Muscle cramps, pain, and stiffness are common. Some patients have enlarged muscles. Features of slow muscle contraction and relaxation occur in 25% of patients; the relaxation phase of muscle stretch reflexes is characteristically prolonged and best observed at the ankle or biceps brachii reflexes. The serum CK level is often elevated (up to 10 times normal). Electromyography is typically normal. Muscle biopsy shows no distinctive morphologic abnormalities. In contrast, patients who are thyrotoxic commonly have proximal muscle weakness, but they rarely

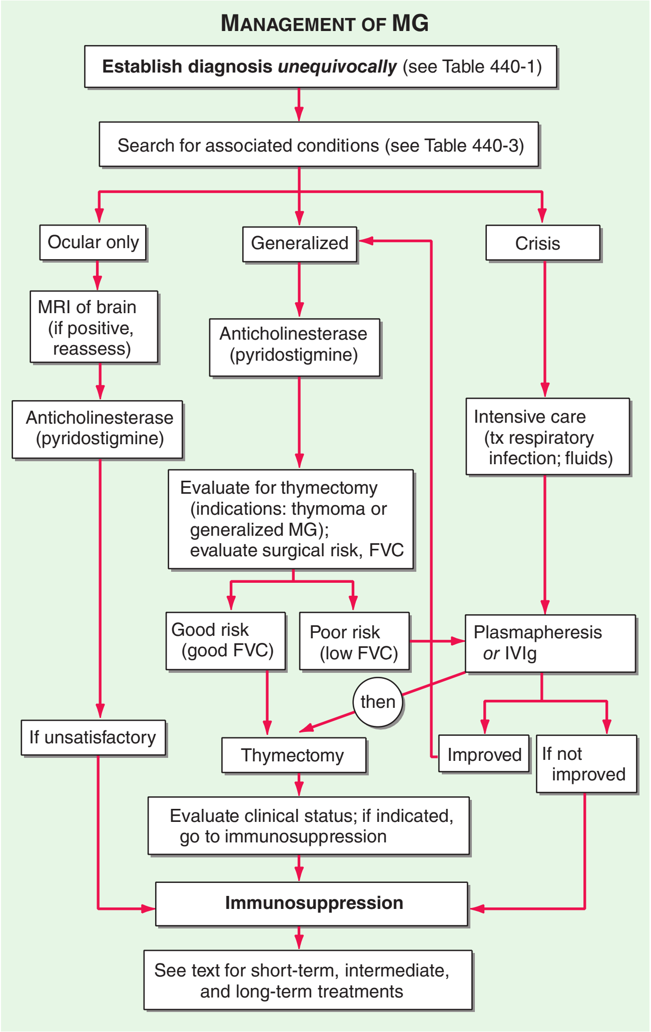

Management of MG
Establish diagnosis unequivocally (see Table 440-1)
Search for associated conditions (see Table 440-3)
Ocular only
Generalized
Crisis
MRI of brain (if positive, reassess)
Anticholinesterase (pyridostigmine)
Anticholinesterase (pyridostigmine)
Intensive care (tx respiratory infection; fluids)
Evaluate for thymectomy (indications: thymoma or generalized MG); evaluate surgical risk, FVC
Good risk (good FVC)
Poor risk (low FVC)
Plasmapheresis or IVIg
then
If unsatisfactory
Thymectomy
Improved
If not improved
Evaluate clinical status; if indicated, go to immunosuppression
Immunosuppression
See text for short-term, intermediate, and long-term treatments

FIGURE X-68 *Abbreviations:* FVC, forced vital capacity; MG, myasthenia gravis.

complain of myopathic symptoms. Proximal muscle weakness, muscle wasting, and brisk muscle stretch reflexes are the main features of hyperparathyroidism. In hypoparathyroidism, an overt myopathy due to hypocalcemia rarely occurs. In primary hyperaldosteronism (*Conn syndrome*), neuromuscular complications are due to potassium depletion. The clinical picture is one of persistent muscle weakness.

X-70. **The answer is A.** *(Chap. 441)* All the drugs listed in question X-70 are known to cause toxic myopathies. The most common toxic myopathies are caused by the cholesterol-lowering agents and glucocorticoids. All classes of lipid-lowering agents have been implicated in muscle toxicity, including HMG-CoA reductase inhibitors (statins), and to a much lesser extent, fibrates, niacin, and ezetimibe. Rarely, symptoms may continue to progress in spite of discontinuing the statin medication. This can represent immune-mediated necrotizing myopathy, as these individuals require aggressive immunotherapy (e.g., prednisone and sometimes other agents) to improve and often relapse when these therapies are discontinued. Interestingly, antibodies directed against HMG-CoA reductase have been identified in many of these cases.

X-71. **The answer is D.** *(Chap. 441)* There are two recognized clinical forms of myotonic dystrophy, both of which are characterized by autosomal dominant inheritance. Myotonic dystrophy type 1 (DM1) is the most common form and the most likely disorder in this patient. Characteristic clinical features of this disorder include a “hatchet-faced” appearance, due to wasting of the facial muscles, and weakness of the neck muscles. In contrast to the muscular dystrophies (Becker and Duchenne), distal limb muscle weakness is more common in DM1. Palatal, pharyngeal, and tongue involvement are also common and produce the dysarthric voice that is frequently heard. The failure of relaxation after a forced handgrip is characteristic of myotonia. Myotonia can also be elicited by percussion of the thenar eminence. In most individuals, myotonia is present by age 5, but clinical symptoms of weakness that lead to diagnosis may not be present until adulthood. Cardiac conduction abnormalities and heart failure are also common in myotonic dystrophy. Diagnosis can often be made by clinical features alone in an individual with classic symptoms and a positive family history. An electromyography would confirm myotonia. Genetic testing for DM1 would show a characteristic trinucleotide repeat on chromosome 19. Genetic anticipation occurs with an increasing number of repeats and worsening clinical disease over successive generations. Myotonic dystrophy type 2 (DM2) causes proximal muscle weakness primarily and is also known by the name proximal myotonic myopathy. Other features of the disease overlap with DM1. Acid maltase deficiency (glucosidase deficiency, or Pompe disease) has three recognized forms, only one of which has onset in adulthood. In the adult-onset form, respiratory muscle weakness is prominent and often is the presenting symptom. As stated previously, Becker and Duchenne muscular dystrophies present with primarily proximal muscle weakness and are X-linked recessive disorders. Becker muscular dystrophy presents at a later age than Duchenne muscular dystrophy and has a more prolonged course. Otherwise, features are similar to one another. Nemaline myopathy is a heterogeneous disorder marked by the threadlike appearance of muscle fibers on biopsy. Nemaline myopathy usually presents in childhood and has a striking facial appearance similar to myotonic dystrophy.

X-72. **The answer is B.** *(Chap. 442)* In the United States, the prevalence of the chronic fatigue syndrome (CFS) is higher among women (~75% of cases), members of minority groups (African and Native Americans), and individuals with lower levels of education and occupational status. Physical inactivity and trauma in childhood tend to increase the risk of CFS in adults. Neuroendocrine dysfunction may be associated with childhood trauma, reflecting a biological correlate of vulnerability. Psychiatric illness and physical hyperactivity in adulthood raise the risk of CFS in later life. Twin studies suggest a familial predisposition to CFS, but research into causative genes has yielded variable results. In a recent systematic review, a number of single nucleotide polymorphisms encoding for tumor necrosis factor-α, interleukin (IL)-1β, IL-6, and IL-4 were found to be associated with increased fatigue in CFS, cancer-related fatigue, and other disease-related fatigue states.

X-73. **The answer is B.** *(Chap. 442)* Cognitive behavioral therapy (CBT) and graded exercise therapy (GET) have been found to be the only beneficial interventions in chronic fatigue syndrome (CFS). Some patient groups argue against these approaches because of the implication that CFS is a purely mental disorder. CBT is a psychotherapeutic approach directed at changing unhealthy disease perpetuating patterns of thoughts and behaviors. It includes educating the patient about the etiologic model, setting goals, restoring fixed bedtimes and wake-up times, challenging and changing fatigue and activity-related concerns, reducing a focus on symptoms, spreading activities evenly throughout the day, gradually increasing physical activity, planning a return to work, and resuming other activities. The intervention, which typically consists of 12–14 sessions spread over 6 months, helps CFS patients gain control over their symptoms. GET targets deconditioning and exercise intolerance and usually involves a home exercise program that continues for 3–5 months. Walking or cycling is systematically increased, with set goals for maximal heart rates. CBT and GET appear to improve fatigue primarily by changing the patient's perception of the fatigue and also by reducing the focus on symptoms. In general, CBT studies tend to yield better improvement rates than GET trials. Not all patients benefit from CBT or GET. Predictors of poor outcome are medical (including psychiatric) comorbidities, current disability claims, and severe pain. CBT offered in an early stage of the illness reduces the burden of CFS for the patient as well as for society in terms of decreased medical and disability-related costs. Full recovery from untreated CFS is rare: the median annual recovery rate is 5% (range, 0–31%), and the median improvement rate is 39% (range, 8–63%). Patients with an underlying psychiatric disorder and those who continue to attribute their symptoms to an undiagnosed medical condition have poorer outcomes. The other listed therapies have been tried in patients with CFS with no proven lasting benefit.

X-74. **The answer is A.** *(Chap. 443)* Significant progress has been made in the genetics of autism spectrum disorders (ASDs), which are a heterogeneous group of neurodevelopmental diseases that share clinical features of impaired social communication and restricted, repetitive patterns of behavior. ASDs are highly heritable; concordance rates in monozygotic twins (~60–90%) are 5- to 10-fold higher than in dizygotic twins and siblings, and first-degree relatives show approximately 10-fold increased risk compared with the general population. ASDs are also genetically heterogeneous. At present, ~70 individual risk genes, along with dozens of submicroscopic deletions and duplications often containing multiple genes, have been identified, almost exclusively through the study of rare, large-effect new (de novo) mutations. All told, genes and genomic regions vulnerable to these types of mutations account for about 20–30% of formerly idiopathic cases that present in the clinic, although none individually accounts for >1%. Amid the genetic heterogeneity that has so far been identified, common themes have emerged that inform pathogenesis of ASDs. For instance, many identified rare mutations are in genes that encode proteins involved in synaptic function and early transcriptional regulation.

X-75. **The answer is A.** *(Chap. 444)* Generalized anxiety disorder (GAD) has a lifetime prevalence of about 5–6% and presents with persistent, excessive and/or unrealistic worry occurring on most days that persists for at least 6 months. The worry typically pervades most aspects of life and is to a degree that it is uncontrollable and causes impairment in social, work, or interpersonal functioning. Associated physical symptoms include tension, restlessness, impaired concentration, insomnia, autonomic arousal, and feeling of being "on edge." Typical onset of symptoms is before the age of 20 although patients may not seek treatment for many years. A history of childhood fears may be present. More than 80% of patients with GAD have a concomitant mood disorder such as major depression or dysthymia or social phobia, but panic attacks (such as 10- to 30-minute episodes including palpitations, shortness of breath, feelings of impending doom) generally do not occur. Comorbid substance abuse, most often with alcohol or sedative/hypnotics, is also common, perhaps as an attempt to self-treat anxiety. Treatment of GAD is most effective when psychotherapy is combined with medications, although complete relief of symptoms is rare. Initial intervention with benzodiazepines is often required for a period of 4–6 weeks. Other medications that are approved by the U.S. Food and Drug Administration for the treatment of GAD are escitalopram, paroxetine, and venlafaxine, although other selective serotonin reuptake inhibitors have been demonstrated in clinical trials to be effective as well typically at doses comparable to the effective dose for major depression. Buspirone is another anxiolytic agent that is nonsedating, does not produce tolerance or dependence, and has no abuse potential. However, it generally has mild effects and takes several weeks to produce results. It has demonstrated best results in individuals with dementia or head injury who develop agitation and/or anxiety. Anticonvulsants with GABAergic properties such as gabapentin, oxcarbazepine, tiagabine, pregabalin, and divalproex also may have efficacy against anxiety.

X-76. **The answer is C.** *(Chap. 444)* There are an estimated 300,000 episodes of acute schizophrenia in the United States annually. This disorder has a high degree of morbidity with many individuals failing to achieve their premorbid level of functioning after an episode of acute schizophrenia. Symptoms of schizophrenia are heterogeneous with perturbations in language, thinking, perception, social activity, affect, and volition. The most typical age of onset is late adolescence and young adulthood. Onset is insidious as individuals progressively experience social withdrawal, perceptual distortion, and often progress to experience frank delusions and hallucinations. As individuals age, the positive symptoms of delusions and hallucinations tend to recede and the negative symptoms of anhedonia, decreased emotional expression, and loss of function become more predominant. In a first episode, antipsychotic agents are effective about 70% of the time. Symptoms may improve with hours or days of dosing, but full remission often takes 6–8 weeks. If medications are discontinued, relapse will occur in 60% of patients within 6 months.

The long-term prognosis of most individuals with schizophrenia is somewhat grim. Prognosis of schizophrenia depends not on symptom severity at initial diagnosis but on the response to antipsychotic medication. A permanent remission rarely occurs. About 10% of schizophrenic patients commit suicide.

X-77. **The answer is D.** *(Chap. 444)* This patient is experiencing her first episode of a panic attack and does not meet criteria for panic disorder. In this situation, no specific treatment is required. The patient should be reassured that she does not have any evidence of a serious medical disorder in a manner that is empathetic and supportive. Panic disorder is a frequently occurring mental disorder with a lifetime prevalence of about 2–3%. Panic attacks begin abruptly, most commonly without an immediate precipitating cause, and peak in severity over 10 minutes. The first episode of panic attack is most often outside the home. The symptoms usually subside spontaneously over the course of an hour. Panic attacks are often accompanied by intense fear and a variety of physical symptoms, including palpitations, dizziness, sweating, shortness of breath, chest pain, and a feeling of impending doom or death. Gastrointestinal distress, paresthesias, and syncope may occur. Panic disorder could be diagnosed if the patient developed recurrent attacks lasting at least 1 month or exhibited excessive worry or change in behavior related to these attacks. If the patient subsequently develops panic disorder, a variety of treatment options can be pursued. The goals of therapy for panic attacks are to decrease the frequency of attacks and severity of symptoms during the attack. Antidepressant medications are the cornerstone of therapy with selective serotonin reuptake inhibitors being the most frequently used class of medication. The dose of medication for panic disorder is typically lower than the antidepressant dose. For fluoxetine, this would be 5–10 mg daily. As these medications take 2–6 weeks to become effective, they are often combined with benzodiazepines early in the course of treatment to alleviate anticipatory anxiety and provide immediate relief of panic symptoms. Alprazolam and clonazepam are common agents used for panic disorder although alprazolam may have more associated dependence with need for escalating doses of medications. In combination with pharmacologic therapy, psychotherapy and education are also useful for the treatment of panic disorder. The therapy often includes breathing techniques, cognitive behavioral therapy, and even homework assignments.

X-78. **The answer is A.** *(Chap. 444)* There are an increasing number of antidepressant medications available in a variety of classes. Selective serotonin reuptake inhibitors are the most commonly used antidepressant drugs. This class of medications includes fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, and escitalopram. These medications are taken once daily and have side effects including sexual dysfunction, headache, and insomnia. Tricyclic antidepressants were commonly used in past decades for treatment of depression. However, overdoses can be lethal, and anticholinergic side effects including dry mouth, constipation, and urinary retention can limit the dose. Medications in the tricyclic class of antidepressants include amitriptyline, nortriptyline, imipramine, desipramine, doxepin, and clomipramine. Mixed norepinephrine/serotonin reuptake inhibitors and receptor blockers are a newer class of medications. These medications are increasing in use as they are quite effective and do not have the same frequency of sexual dysfunction. Medications in this class include venlafaxine, desvenlafaxine, duloxetine, and mirtazapine. Monoamine oxidase inhibitors were once a common antidepressant class of medication, but these medications are now only rarely used. There is a wide range of drug and food interactions that can lead to hypertensive crises. Examples of medication in this class include phenelzine, tranylcypromine, and isocarboxazid. A final class of antidepressants is called simply mixed action drugs and includes trazodone, bupropion, and nefazodone.

X-79. **The answer is E.** *(Chap. 444)* Post-traumatic stress disorder (PTSD) was only added as a discrete disorder in 1980. The diagnostic criteria for PTSD are long and require that an individual experiences an event where there was an actual or perceived threat of death or serious injury and that the individual's reaction included intense fear or helplessness. Following the event, the individual continues to re-experience the event and avoids stimuli associated with the trauma. In association with this, there is also often a generalized withdrawal and decrease in responsiveness. At the same time, the patient exhibits an increase in arousal that is often exhibited by insomnia, irritability, hypervigilance, and difficulty concentrating. Treatment of PTSD is almost always multifactorial, including both pharmacotherapy and psychotherapy. It is not uncommon for an individual with PTSD to develop dependence on drugs or alcohol as an attempt to control the symptoms, and any substance abuse issues need to be treated simultaneously as well. This patient's treatment would include avoidance of alcohol and most intensive substance abuse treatment as needed. Treatment with antidepressant medications can decrease anxiety and avoidance behaviors. Trazodone is often given at night for its sedating properties. Psychotherapeutic strategies include cognitive behavioral therapy to overcome avoidance behaviors as well.

X-80. **The answer is B.** *(Chap. 444)* Fifteen percent of the population will experience at least one episode of major depression over the course of a lifetime, and most episodes of major depression are treated by primary care practitioners. Treatment can be any of a number of medications across a variety of classes. Despite the popularity of newer antidepressants, there is no evidence that these medications are more efficacious than older drugs like tricyclic antidepressants. Indeed, 60–70% of patients will respond to any drug chosen if given in a sufficient dose for 6–8 weeks. However, up to 40% of patients treated at primary care offices discontinue treatment if there has not been a response within 1 month. Once a patient has been on treatment for ~2 months, the response should be evaluated, and if there has been an insufficient response, a dosage increase should be considered. In this patient, a dosage increase yielded control of depressive symptoms at 4 months. Once control of symptoms has been achieved, the drug should be continued for an additional 6–9 months to prevent relapse. If a patient experiences any additional episodes of major depression, he will likely require indefinite maintenance treatment as it is recommended that anyone with more than two episodes of major depression continue treatment indefinitely.

X-81. **The answer is B.** *(Chap. 444)* Patients with somatic symptom disorder are frequently subjected to many diagnostic tests and exploratory surgeries in an attempt to find their "real" illness. Such an approach is doomed to failure and does not address the core issue. Successful treatment is best achieved through behavior modification, in which access to the physician is tightly regulated and adjusted to provide a sustained and predictable level of support that is less clearly contingent on the patient's level of presenting distress. Visits can be brief and should not be associated with a need for a diagnostic or treatment action. Although the literature is limited, some patients may benefit from antidepressant treatment. Any attempt to confront the patient usually creates a sense of humiliation and causes the patient to abandon treatment from that caregiver. A better strategy is to introduce psychological causation as one of a number of possible explanations in the differential diagnoses that are discussed. Without directly linking psychotherapeutic intervention to the diagnosis, the patient can be offered a face-saving means by which the pathologic relationship with the health care system can be examined and alternative approaches to life stressors developed. Specific medical treatments also may be indicated and effective in treating some of the functional consequences of conversion disorder.

X-82. **The answer is F.** *(Chap. 445)* About 20% of all patients have an alcohol use disorder, even in affluent locales. Patients should be screened for an alcohol use disorder by asking specific questions regarding alcohol consumption, although many patients may minimize their alcohol use. The patient in the scenario presented reports daily alcohol consumption and some symptoms of an alcohol use disorder, including blackouts from drinking and frequent hangovers while working. Laboratory tests may be helpful in this situation as they can be elevated in individuals who regularly consume six or more drinks daily. The two tests with the greatest sensitivity and specificity (≥60%) are the gamma-glutamyl transferase and the carbohydrate-deficient transferrin. Using the combination of these tests at the limits stated in the question is more likely to be accurate than either test alone. Other blood tests that may be useful include high-normal mean corpuscular volume >91 μm^3 and elevated serum uric acid 7 mg/dL. Elevations in aspartate aminotransferase or alanine aminotransferase are neither sensitive nor specific.

X-83. **The answer is A.** *(Chap. 445)* Alcohol is primarily absorbed through the proximal small intestine, but small amounts can also be absorbed in the mouth, esophagus, stomach, and large intestines as well. Several factors can increase the rate of absorption. One factor that increases absorption is rapid gastric emptying, which can be induced by concurrent consumption of carbonated beverages. Another factor that increases absorption from the gut to the blood is the ingestion of alcohol in the absence of other calorie sources such as proteins, fat, or carbohydrates. A final factor that can increase absorption is to drink alcohol that is diluted to a modest concentration (~20% or less). At high alcohol concentrations, absorption is decreased although high blood levels may be achieved because the amount of alcohol ingested is high.

X-84. **The answer is C.** *(Chap. 445)* Alcohol has effects on many neurotransmitters in the brain. The predominant effect of alcohol lies in its ability to cause release of gamma-aminobutyric acid (GABA) and acts primarily at the $GABA_A$ receptors. GABA is the primary inhibitory neurotransmitter in the brain and is associated with the sedative effects of alcohol. Many other drugs affect the GABA system including benzodiazepines, nonbenzodiazepine sleep aids such as zolpidem, anticonvulsants, and muscle relaxants. The euphoric effects of alcohol consumption are related to increases in dopamine, which is common to all pleasurable activities. The effects on dopamine are thought to be important in alcohol craving and relapse. In addition, alcohol alters opioid receptors and can lead to a release of beta endorphins during acute ingestion. In addition to these effects, alcohol also inhibits postsynaptic N-methyl-D-aspartate excitatory glutamate receptors. Glutamate is the primary excitatory neurotransmitter of the brain, and its inhibition further contributes to the sedative effects of alcohol. Additional important effects on neurotransmitters include increased serotonin activity and decreased nicotinic acetylcholine receptors.

X-85. **The answer is D.** *(Chap. 445)* The acute effects of any drug depend on many factors including amount consumed and absorbed, presence of other drugs, and past experience with the drug. In an individual who is naïve to alcohol, drug levels as low as 0.02 g/dL can lead to a decrease in inhibitions and a slight feeling of intoxication. In the United States, "legal" intoxication occurs at a blood alcohol level of 0.08 g/dL in most states. At this level, decreases in cognitive and motor abilities are seen. Once an alcohol level of 0.20 g/dL is achieved, an individual is obviously impaired with slurred speech, poor judgment, and impaired coordination. Light coma and depression of respiratory rate, blood pressure, and pulse occur at levels around 0.30 g/dL, and death is likely to occur at levels of 0.40 g/dL. However, in individuals who drink heavily, tolerance to alcohol begins to develop. After a period of 1–2 weeks of daily alcohol consumption, liver metabolism of alcohol increases by as much as 30%, but disappears quite quickly with abstinence. Cellular or pharmacodynamic tolerance also occurs and refers to the neurochemical changes that allows an individual to maintain more normal physiologic functioning despite the presence of alcohol.

X-86. **The answer is B.** *(Chap. 445)* Individuals with alcohol dependence are susceptible to alcohol withdrawal when alcohol intake is stopped abruptly. The individual in this case scenario is likely alcohol dependent given his large amount of alcohol intake on a daily basis. Symptoms of alcohol withdrawal can range from mild tremulousness to hallucinations, seizures, or development of delirium tremens. Other clinical features of alcohol withdrawal include anxiety, insomnia, and autonomic nervous system overactivity manifested as tachycardia, tachypnea, elevated blood pressure, and fever. This patient exhibits symptoms of the more severe delirium tremens, with mental confusion, agitation, and fluctuating levels of consciousness. While minor symptoms of alcohol withdrawal may begin as soon as 5–10 hours after cessation of alcohol intake, the symptoms do not peak for 48–72 hours, putting this patient in the appropriate time frame for alcohol withdrawal. The best approach for the alcohol-dependent patient who abruptly stops all alcohol intake is to take a prophylactic approach and screen early for symptoms of alcohol withdrawal. Tools such as the Revised Clinical Institute for Withdrawal Assessment for Alcohol may help clinicians and nurses screen for early development of symptoms and allow intervention before symptoms escalate. In this setting, most experts recommend use of oral long-acting benzodiazepines such as chlordiazepoxide or diazepam beginning on the first day. However, in this case, the patient received no such treatment and is now experiencing severe alcohol withdrawal and delirium tremens. IV medications that have a rapid onset of action and can be titrated for more aggressive symptom management are often employed in this setting. Thus, use of IV lorazepam or diazepam is preferred in this patient. Following an initial bolus, repeated doses can be used in short intervals until the patient is calm but arousable. In some instances, a continuous infusion may be required although bolus dosing is preferred. In the most severe cases, propofol or barbiturates may be required although the patient would most likely need to be intubated for airway protection with use of these medications. The other options listed are not appropriate for initial management of this patient. IV fluids and thiamine had been administered since hospital admission. Administration of glucose-containing fluids without thiamine in the alcohol-dependent patient can precipitate Wernicke encephalopathy, which would present with ophthalmoparesis, ataxia, and encephalopathy. Given the patient's fever, an infectious etiology can be considered, and it would be appropriate to perform blood cultures in this patient. However, given the clear symptoms of alcohol withdrawal and lack of necrotizing pancreatitis on CT abdomen, empiric treatment with antibiotics is not required at this time. Likewise, without focal neurologic findings, a head CT would be a low-yield diagnostic procedure that would be difficult to perform in the patient's current agitated condition and would only delay appropriate therapy. Finally, restraints are best avoided if the patient's safety can be ensured through appropriate use of benzodiazepines as restraints are only likely to make the patient's agitation worse and may lead to iatrogenic harm. Haloperidol may have some sedative effect on the patient, but could lead to torsades de pointe arrhythmia as this patient is at risk for electrolyte deficiencies from his alcoholism and pancreatitis.

X-87. **The answer is D.** *(Chap. 445)* In individuals recovering from alcoholism, several medications may have a modest benefit in increasing abstinence rates. The two medications with the best risk-benefit ratio are acamprosate and naltrexone. Acamprosate inhibits N-methyl-D-aspartate receptors, decreasing symptoms of prolonged alcohol withdrawal. Naltrexone is an opioid antagonist that can be administered orally or as a monthly injection. It is thought to act by decreasing activity in the dopamine-rich ventral tegmental area of the brainstem and subsequently decreasing the pleasurable feelings associated with alcohol consumption. There is some research to suggest that the use of these medications in combination may be more effective than either one alone. Disulfiram is an aldehyde dehydrogenase inhibitor that has been used for many years in the treatment of alcoholism. However, it is no longer a commonly used drug due to its many side effects and risks associated with treatment. The primary mechanism by which it acts is to create negative effects of vomiting and autonomic nervous system hyperactivity when alcohol is consumed concurrently with use of the medication. As it inhibits an enzyme that is part of the normal metabolism of alcohol, it allows the build-up of acetaldehyde, which creates these symptoms. Because of the autonomic side effects, it is contraindicated in individuals with hypertension, a history of stroke, heart disease, or diabetes mellitus.

X-88. **The answer is C.** *(Chap. 446)* In 2015, for example, 3.8 million individuals in the United States were current misusers of pain relievers. More concerning, during 2015 >20,000 overdose deaths involved opioids with an additional 12,990 overdose deaths related to heroin alone. These numbers continue to increase and have accelerated due to mixing high potency fentanyl derivatives with heroin. The accelerating death rates are partially because reversal of fentanyl overdoses can require severalfold larger doses of naloxone than the doses in the intranasal devices used for nonmedical street resuscitations. According to the most recent World Drug Report, opioid misuse causes the greatest global burden of morbidity and mortality; disease transmission; increased health care, crime, and law enforcement costs; and less tangible costs of family distress and lost productivity.

X-89. The answer is E. *(Chap. 446)* Symptoms of opioid withdrawal begin 8–10 hours after the last dose; lacrimation, rhinorrhea, yawning, and sweating appear first. Restless sleep followed by weakness, chills, gooseflesh ("cold turkey"), nausea and vomiting, muscle aches, and involuntary movements ("kicking the habit"), hyperpnea, hyperthermia, and hypertension occur in later stages of the withdrawal syndrome. The acute course of withdrawal may last 7–10 days. A secondary phase of protracted abstinence lasts for 26–30 weeks and is characterized by hypotension, bradycardia, hypothermia, mydriasis, and decreased responsiveness of the respiratory center to carbon dioxide.

X-90. The answer is D. *(Chap. 446)* Besides the brain effects of opioids on sedation and euphoria and the combined brain and peripheral nervous system effects on analgesia, a wide range of other organs can be affected. The release of several pituitary hormones is inhibited, including corticotropin-releasing factor (CRF) and luteinizing hormone, which reduces levels of cortisol and sex hormones and can lead to impaired stress responses and reduced libido. An increase in prolactin also contributes to the reduced sex drive in males. Two other hormones affected are thyrotropin, which is reduced, and growth hormone, which is increased.

X-91. The answer is E. *(Chap. 446)* While most opioids have effects that last hours, naloxone has a considerately shorter half-life. Because naloxone only lasts a few minutes to hours and most opioids last considerably longer, an IV naloxone drip or repeated doses with close monitoring is frequently employed to provide a continuous level of antagonism for 24–72 hours depending on the opioid used in the overdose (e.g., morphine vs methadone) (Table X-91). Close observation is warranted and he may require transfer to an intensive care unit and consideration of intubation for airway protection. Flumazenil is a benzodiazepine antagonist and will not help reverse the opioid depressant effect on respiratory drive.

TABLE X-91 Management of Opioid Overdose

Establish airway. Intubation and mechanical ventilation may be necessary.
Naloxone 0.4–2.0 mg (IV, IM, or endotracheal tube). Onset of action with IV is ~1–2 min.
Repeat doses of naloxone if needed to restore adequate respiration or a continuous infusion of naloxone can be used.
One-half to two-thirds of the initial naloxone dose that reversed the respiratory depression is administered on an hourly basis. (Note: naloxone dosing is not necessary if the patient has been intubated.)

X-92. The answer is E. *(Chap. 447)* Cocaine is a powerful stimulant drug made from the cocoa plant. It has local anesthetic, vasoconstrictor, and stimulant properties. Cocaine is a Schedule II drug, which means that it has high potential for abuse but can be administered by a physician for legitimate medical uses, such as local anesthesia for some eye, ear, and throat surgeries (Table X-92). Given the extensive pulmonary vasculature, smoked or inhaled cocaine reaches the brain very quickly and produces a rapid and intense (yet transient) high, which enhances its addictive potential. Cocaine binds to the dopamine (DA) transporter and blocks DA reuptake, which increases synaptic levels of the monoamine neurotransmitters DA, norepinephrine, and serotonin, in both the central nervous system and the peripheral nervous system. Use of cocaine, like other drugs of abuse, induces long-term changes in the brain. Animal studies have shown adaptations in neurons that release the excitatory neurotransmitter glutamate after cocaine exposure. The complications of cocaine relate to its metabolic and vasoactive effects.

TABLE X-92 Complications of Cocaine Use

Cardiovascular	Acute • Arterial vasoconstriction • Thrombosis • Tachycardia • Hypertension • Increased myocardial oxygen demand • Increased vascular shearing forces • Coronary vasoconstriction • Cardiac ischemia • Left ventricular dysfunction/heart failure (high blood concentrations) • Supraventricular and ventricular dysrhythmias • Aortic dissection/rupture Chronic • Accelerated atherogenesis • Left ventricular hypertrophy • Dilated cardiomyopathy
Central and peripheral nervous	• Hyperthermia • Psychomotor agitation • Tremor • Hyperreflexia • Hypertonia • Headache • Seizures • Coma • Intracranial hemorrhage • Focal neurologic symptoms
Pulmonary	• Angioedema (inhaled) • Pharyngeal burns (inhaled) • Pneumothorax • Pneumomediastinum • Pneumopericardium • Reversible airway disease exacerbations • Bronchospasm • Shortness of breath ("crack lung") • Tachypnea • Pulmonary infarction
Gastrointestinal	• Perforated ulcers • Ischemic colitis • Bowel infarction • Impaction (body packing) • Hepatic enzyme elevation
Renal	• Metabolic acidosis • Renal infarction • Rhabdomyolysis
Endocrine	• Impotence • Gynecomastia • Menstrual function disruptions • Hyperprolactinemia
Other	• Diaphoresis • Irritability • Insomnia • Bruxism • Stereotypy • Splenic infarction • Acute angle-closure glaucoma • Vasospasm of the retinal vessels (unilateral or bilateral vision loss) • Mydriasis • Madarosis • Abruptio placentae

X-93. **The answer is E.** *(Chap. 447)* Hallucinogens are a diverse group of drugs causing alteration of thoughts, feelings, sensations, and perceptions. Their use in religious and spiritual rituals goes back centuries. Hallucinogens can be found naturally in plants and mushrooms, or can be human-made. They include ayahuasca (a tea made from Amazonian plants containing dimethyltryptamine [DMT], the primary mind-altering ingredient), DMT (aka Dimitri, can also be synthesized in a lab), LSD (clear or white odorless material made from lysergic acid found in rye and other grain fungus), peyote (mescaline, derived from a small, spineless cactus or made synthetically), and 4-phosphoryloxy-N, N-dimethyltryptamine (psilocybin, comes from certain South and North American mushrooms). A subgroup of hallucinogens produces the added sensation of feeling out of control or disconnected from one's body or surroundings. These include DXM (an over-the-counter cough suppressant, when used in high doses), ketamine (a human and veterinary anesthetic), PCP (cyclohexylamine derivative and dissociative anesthetic), and *Salvia divinorum* (salvia, a Mexican and Central and South American plant). There are currently no medications for the treatment of hallucinogen addiction approved by the U.S. Food and Drug Administration. Research on behavioral treatments for hallucinogen addiction is underway.

X-94. **The answer is B.** *(Chap. 448)* While declining in prevalence, cigarette smoking and use of other nicotine-containing products remain a significant contributor to premature death in the United States. This accounts for about one of every five deaths in the United States for a total of 400,000 annually. Approximately 40% of cigarette smokers will die prematurely due to the habit unless they are able to quit. The primary causes of premature death related to cigarette smoking are cardiovascular diseases including both myocardial infarction and stroke; chronic obstructive pulmonary disease (COPD); and myriad cancers including lung, oral, esophageal, urogenital, and pancreatic cancer. Cigarette smoking promotes both large- and small-vessel vascular disease. Approximately 90% of peripheral vascular disease in the non-diabetic population can be attributed to cigarette smoking. In addition, 50% of aortic aneurysms, 20–30% of coronary artery disease, and 10% of ischemic and hemorrhagic strokes are caused by cigarette smoking. Moreover, if additional cardiac risk factors are present, the incremental risk added by cigarette smoking is multiplicative. As mentioned above, cigarette smoking increases the risk of many different cancers and not only those of the respiratory tract. The digestive tract appears particularly susceptible to the effects of cigarette smoking as cigarette smoking has been linked to esophageal, stomach, pancreatic, liver, and colorectal cancer. Urogenital cancers are also increased in cigarette smokers with increases in both kidney and bladder cancer. In women, cervical cancer is also increased among smokers. Interestingly, however, uterine cancer may be decreased among post-menopausal woman who smoke. Cigarette smoking is responsible for 90% of COPD. Cigarette smoking induces chronic inflammation in the small airways, although most do not develop symptomatic respiratory disease. Chronic inflammation and narrowing of the small airways and destruction of the alveoli lead to symptoms of COPD and emphysema in 15–25% of smokers. In any given year, more than half of smokers would like to quit smoking. However, only 6% quit for 6 months, and less than 3% remain abstinent at 3 years. Most individuals have to make multiple attempts to quit before being successful and are more likely to be successful if advised to quit by a physician. Other triggers for smoking cessation include an acute illness, the cost of cigarettes, media campaigns, and workplace smoking restrictions.

X-95. **The answer is E.** *(Chap. 448)* Smoking cessation is more likely to be successful when an individual is advised to quit by a physician and has a supervised smoking cessation plan. At every medical visit, all patients should be asked whether they smoke, how much they smoke, and whether they are interested in quitting. Even patients who state that they are not interested in quitting should receive a clear message from their provider that smoking is an important health hazard and offered assistance with quitting in the future. For those interested in quitting, negotiating a quit date is an important step in the process, and close follow-up with office contact near the quit date is an important part of the process. In addition, sometimes a more intensive counseling approach may be necessary. Current recommendations are to offer pharmacologic therapy with either nicotine replacement therapy (NRT) or varenicline. A variety of NRT is available, including transdermal patches, nasal inhaler, gum, oral inhaler, or lozenge, with success rates of 1.5 to 2.7 compared with no intervention. Varenicline is an oral partial agonist of the nicotinic acetylcholine receptor that has a published success rate of 2.7 compared with no intervention. There has been some concern regarding use of varenicline in individuals with severe psychiatric illness including suicidal ideation, but this individual does not meet this level of concern. With planned close follow-up, varenicline should be considered an available option for this patient.

X-96. **The answer is B.** *(Chap. 448)* Smokers regulate their blood levels of nicotine by adjusting the frequency and intensity of their tobacco use. Smokers can compensate for the lower levels of nicotine in low-yield cigarettes by smoking more cigarettes or by adjusting their smoking technique with a deeper inhalation and breath-hold. Therefore, smoking low-yield cigarettes is not a reasonable alternative to smoking cessation. Moreover, there is no difference in the harmful physical effects of smoking or in the potential for drug interactions. Finally, although not definitively proven, there is some thought that the rise in adenocarcinoma of the lung over the past 50 years is associated with introduction of the low-tar cigarette and the resultant change in smoking behavior associated with this.